The dilemma of a left ventricular assist device explantation: A decision analysis

Diego H Delgado MD¹, Heather J Ross MD MHSc¹, Vivek Rao MD PhD²

DH Delgado, HJ Ross, V Rao. The dilemma of a left ventricular assist device explantation: A decision analysis. *Can J Cardiol* 2007;23(8):657-661.

BACKGROUND: Left ventricular assist devices (LVADs) are an important adjunct to the management of end-stage heart failure patients. Uncertainty remains regarding whether to remove an LVAD in a clinically stable, asymptomatic patient who displays signs of ventricular recovery.

OBJECTIVES: To evaluate, from a patient's perspective, the quality-adjusted life expectancy of an LVAD explantation.

METHODS: A Markov state transition model was used to assess the benefits of two strategies: remove an LVAD or continue the LVAD support. Effectiveness was measured in quality-adjusted life months. Utility and probability scores were derived from the literature and expert opinion. The base case focused on a 35-year-old man with dilated cardiomyopathy, an implantable LVAD and signs of ventricular recovery, with New York Heart Association class I heart failure symptoms.

RESULTS: In the base case, continuing LVAD support was strongly preferred and improved quality-adjusted life expectancy by nine quality-adjusted life months. In sensitivity analyses for the utility post-transplant, removal of the device would have been preferred if the utility was less than 0.7. The model was also sensitive to the probability of late complications post-LVAD implantation. As the probability of complications increased (greater than 28%), the preferred strategy was to remove the LVAD.

CONCLUSIONS: Continuing LVAD support in asymptomatic patients with signs of ventricular recovery appears to be the preferred strategy for conveying greater quality-adjusted life months compared with LVAD explantation. As the probability of complications after LVAD implantation increases, the preferred strategy is to remove the LVAD.

Key Words: Congestive heart failure; Health economics; Heart assist device

Mechanical circulatory support is an important adjunct in the management of end-stage heart failure patients. It has been shown to be effective as short-term therapy, as a bridge to transplantation and as permanent cardiac support (1). However, given the shortage of donor organs, all patients undergoing left ventricular assist device (LVAD) support should be systematically evaluated for evidence of myocardial recovery (2,3). Several studies have found that LVAD support is associated with beneficial hemodynamic, neurohormonal, physiological, cellular and molecular changes, supporting the use of an LVAD as a bridge to recovery (4,5).

Despite the existing evidence in support of myocardial improvement in patients receiving LVAD assistance, neither

Le retrait des dispositifs d'assistance ventriculaire gauche : Le dilemme et l'analyse de la décision

CONTEXTE : Les dispositifs d'assistance ventriculaire gauche (DAVG) constituent une intervention d'appoint importante dans le traitement de l'insuffisance cardiaque terminale. Cependant, il subsiste des doutes sur la pertinence de retirer le DAVG chez les patients cliniquement stables et asymptomatiques, qui montrent des signes de récupération ventriculaire.

BUT : L'étude avait pour but d'évaluer, du point de vue du patient, l'espérance de vie pondérée par la qualité de l'existence, liée au retrait du DAVG.

MÉTHODE : Nous nous sommes appuyés sur un modèle markovien de transition d'états pour évaluer les bienfaits de deux stratégies : le retrait du DAVG ou son maintien en place. L'efficacité a été mesurée en mois de vie pondérée par la qualité. Les scores d'utilité et de probabilités ont été tirés de la documentation et d'avis d'experts. Le scénario de référence était celui d'un homme de 35 ans, porteur d'une myocardiopathie dilatée et d'un DAVG implantable, qui présentait des signes de récupération ventriculaire, accompagnés de symptômes d'insuffisance cardiaque de classe 1 selon la *New York Heart Association*.

RÉSULTATS : Dans le scénario de référence, le maintien du dispositif était préféré de loin et permettait de prolonger l'espérance de vie pondérée par la qualité de l'existence de neuf mois de vie pondérée. Dans les analyses de sensibilité relativement à l'utilité de la pose, il était préférable de retirer le DAVG si le poids de l'utilité était inférieur à 0,7. Le modèle s'est également montré sensible aux complications tardives du port du dispositif. Comme les probabilités de complications augmentaient (supérieures à 28 %), la meilleure stratégie s'est révélée celle du retrait.

CONCLUSIONS : Le maintien en place du DAVG chez les patients asymptomatiques, qui montrent des signes de récupération ventriculaire semble la meilleure stratégie en ce qui concerne le prolongement de la vie pondérée par la qualité, par rapport au retrait de l'appareil. Par contre, à mesure qu'augmentent les probabilités de complications, il est préférable de retirer le DAVG.

the incidence of sustained improvement nor the functional assessment that may better predict sustained myocardial improvement are well known. Recently, some studies have demonstrated that dobutamine stress echocardiography, in conjunction with a hemodynamic assessment, predicts improvement in myocardial function in patients with end-stage heart failure on LVAD support and predicts which of these patients can ultimately undergo LVAD removal with acceptable survival (6,7). Most patients considered for LVAD explantation include those who have signs of myocardial recovery and/or have a clear indication for LVAD explantation (eg, active life-threatening infection). However, uncertainty remains whether to remove an LVAD in an asymptomatic patient (New York Heart

¹Division of Cardiology and Transplantation; ²Division of Cardiovascular Surgery, Toronto General Hospital, Toronto, Ontario

Correspondence and reprints: Dr Diego H Delgado, New Clinical Services Building, IIC-1201, 585 University Avenue, Toronto, Ontario

M5G 2N2. Telephone 416-340-3940, fax 416-340-4134, e-mail diego.delgado@uhn.on.ca

Received for publication November 8, 2005. Accepted June 20, 2006

Figure 1) The Markov model structure. LVAD Left ventricular assist device

Association [NYHA] class I) who has no evidence of end-organ dysfunction and displays signs of ventricular recovery. Should we consider removing the device, or should we continue the support until a heart transplant is available?

Decision analysis is an approach used to assess treatment options in situations in which no specific data from randomized trials are available (8). We used decision analysis to estimate the benefits, in terms of life expectancy and quality of life, between two strategies – removing the LVAD versus continuing the LVAD support. Decision analysis is an appropriate method to quantify the relative value of these two strategies in the management of patients supported with a mechanical assist device.

METHODS

A Markov decision analysis was created to assess the benefits of two strategies – removing an LVAD or continuing the LVAD support. A Markov decision analysis synthesized the probabilities of multiple clinical outcomes in the assessment of competing treatment strategies (9).

The Markov model structure used in the present study is shown in Figure 1. The model evaluates LVAD removal or LVAD

continuation as an initial decision in a stable and asymptomatic patient who has no evidence of end-organ dysfunction and has signs of left ventricular recovery. Regardless of the decision made, patients can ‘do well’ (remain asymptomatic) or ‘do unwell’ (develop symptoms). This chance node determines which patients would and would not ultimately remain stable if their LVADs were to be explanted (Figure 1).

Seven health states are considered in this model: stable patients with an LVAD, symptomatic patients with an LVAD, stable patients without an LVAD, symptomatic patients without an LVAD, patients undergoing transplantation, patients post-heart transplantation and patients who have died.

State transitions

There are potential transitions to other health states during each Markov cycle (one month in our model; Figure 2) that depend on a patient's current state of health:

- Patients who remain stable with an LVAD may live or die of unrelated causes. If they survive, they may receive a transplant. If a transplant is not available, they may remain

Figure 2) Schematics of the health transitions. LVAD Left ventricular assist device

asymptomatic or develop symptoms. In those who survive, LVAD complications may or may not occur, and subsequently, these patients may live or die.

- Symptomatic patients with an LVAD may live or die of unrelated causes. If they survive and do not receive a transplant, they may live and develop LVAD complications and subsequently live or die.
- Stable patients without an LVAD may live or die of unrelated causes. If they survive, they may develop symptoms. If they develop symptoms, they may receive a transplant and subsequently live or die.
- Symptomatic patients without an LVAD may live or die of unrelated causes. If they survive, they may receive a transplant.
- Patients who receive a transplant may survive and experience acute complications or die.
- Patients in a post-transplant state may live and experience chronic complications or die of unrelated causes.
- Patients who die are an absorbing state.

The case-based analysis considered a 35-year-old man with idiopathic dilated cardiomyopathy who had an LVAD implanted. His current status is asymptomatic (New York Heart Association class I); he has no evidence of end-organ dysfunction, and has echocardiographic and hemodynamic signs of ventricular recovery.

Assumptions

Several assumptions were made to simplify the decision analysis. The length of each Markov cycle was one month. Time-dependent variables (probability of a transplant, probability of developing symptoms after LVAD implantation, probability of chronic complications post-transplant) and time-independent variables (probability of complications post-LVAD, probability of death without an LVAD, probability of death post-transplant and probability of developing symptoms with an LVAD) were incorporated. Based on previous publications and the authors' own experience, a median time of six months for developing symptoms after LVAD removal was assumed (6,17,25,26). A median of four months for time to transplant based on the authors' own experience was used.

Patients entering the model were assumed to be free from non-cardiac life-threatening morbidities. There were no explicit indications to explant the LVAD, such as infection or stroke.

Several studies have proposed clinical, hemodynamic, neuro-hormonal and/or echocardiographic assessment of ventricular

TABLE 1
Input variables and their sources

Variable	Value	Range	Source
Age-related mortality	Age-specific	–	10
Annual rate of death in New York Heart Association class IV patients	0.45	–	11,12
Probability of death post-transplant	0.15	0.14–1.16	13
Probability of death on an LVAD with symptoms	0.64	–	14
Probability of complications related to an LVAD	0.20	0.15–0.35	14-16,24
Sensitivity of LVAD weaning protocol	0.45	0.35–0.65	7,17,18
Specificity of LVAD weaning protocol	0.55	0.45–0.7	7,17,18
Utility of being stable with an LVAD	0.7	0.66–0.93	19
Utility of being symptomatic with an LVAD	0.3	–	Assumed
Utility of being stable without an LVAD	0.9	0.8–1	20,21
Utility of being symptomatic without an LVAD	0.2	0.15–0.3	20,21
Utility of heart transplant	0.9	0.76–0.95	22,23
Utility post-heart transplant	0.8	0.65–0.9	22,23

LVAD Left ventricular assist device

recovery of patients on LVAD support (4,6,7). Based on these publications, it was assumed that the overall sensitivity and specificity of these tests for predicting ventricular recovery were 45% and 55%, respectively. These values were incorporated into the model.

Patients were mechanically assisted with a HeartMate Ventricular Assist Device (Thoratec, USA) for at least three months before consideration for a ventricular recovery assessment.

It was also assumed that patients undergoing heart transplantation (with or without an LVAD bridge to transplantation) may develop acute complications (infection and rejection) within the first 12 months after transplantation. Patients may then experience chronic complications (cancer or graft vasculopathy).

Input variables

For the construction of a decision analysis model, an important step is to assign quantitative estimates to the probabilities of each possible outcome. These are derived from internally and externally valid clinical studies, or from expert opinion when published reports are not helpful. The utilities are preferences under conditions of uncertainty; these are quantitative expressions, on a scale from zero to one, of the strength of an individual's preferences for that outcome. The degree to which an outcome is preferred, as reflected in the utility scale, represents the 'goodness' of that outcome.

All input variables and their sources are shown in Table 1. Due to a lack of information regarding utilities and other input variables for this model, some value ranges are missing.

Age-specific mortality was obtained from the 1998 life tables (10). The annual rate of death of patients in NYHA class IV was obtained from previous reports (11,12). The mortality post-transplant was modelled after the International Society for Heart and Lung Transplantation database (13).

The risk of developing complications after LVAD implantation was obtained from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH) trial and other publications (14-16).

The sensitivity and specificity of the LVAD weaning protocol was modelled after previous publications (7,17,18).

TABLE 2
Sensitivity analyses

Parameter	Base case	Range	Threshold value
Utility post-transplant	0.8	-0.65-0.9	0.7
Probability of complications post-LVAD implantation	0.2	0.15-0.35	0.28

LVAD Left ventricular assist device

Changes between health states may occur rapidly (weeks to months); therefore, the length of each Markov cycle for this model was one month. For the same reason, quality-adjusted life months (QALMs) were calculated for each management strategy. The utility for each health state was based on literature review and expert opinion (Table 1). (Two cardiac transplantation physicians, one cardiac surgeon and two acute care nurse practitioners specialized in cardiac transplantation were interviewed.) The utility of being supported with an LVAD was modelled after Moskowitz et al (19). The utility of heart failure patients without an LVAD was extracted from previous publications (20,21).

Sensitivity analysis

A one-way sensitivity analysis was performed to test the stability of this model, with a variation of selected model input parameters within a reasonable range. Decision analyses were performed using DATAPro (TreeAge Software Inc, USA).

RESULTS

For a hypothetical 35-year-old man with idiopathic dilated cardiomyopathy, an implanted LVAD, signs of ventricular recovery and NYHA class I heart failure symptoms, the 'continue' LVAD strategy resulted in an expected 66 QALMs, whereas the 'remove' LVAD strategy resulted in 57 QALMs. Therefore, given the structure of the model and the baseline probability and utility values, continuation of LVAD support in appropriately selected patients was the preferred strategy.

One-way sensitivity analyses were performed on all probabilities and utilities over the entire range of probabilities (0 to 1) to assess the robustness of the model (Table 2).

The model was sensitive to the utility post-heart transplantation. The threshold utility level was 0.7, indicating that if the utility level was less than 0.7, the 'remove' LVAD strategy is preferred.

The model was also sensitive to the probability of late complications post-LVAD implantation. As the probability of complications increased (threshold 0.28), the strategy preference changed from 'continue' to 'remove' the LVAD.

The model shows that patients who may undergo heart transplantation within 16 months post-LVAD implantation (eg, patients with blood type A) should continue LVAD support. On the other hand, if the expected time to transplantation was more than 16 months, the strategy preference changed to 'remove' the LVAD.

Treatment decisions were not significantly affected by other variables over a wide range of probabilities or utilities.

DISCUSSION

The clinical management of patients with a mechanical assist device remains complex, particularly when patients present with complications related to the device (24). Among patients with dilated cardiomyopathy who had device explantation for recovery, a variable number (30% to 50%) developed recurrent heart

failure after device removal, requiring relisting for transplantation or repeat LVAD placement (26,27). In addition, the optimum weaning protocol has yet to be determined. LVAD as a bridge to recovery represents an intriguing and enticing possibility in heart failure. We believe that a decision analysis approach may be useful to clarify the dilemma of explanting an LVAD.

The situation is even more complex when a clinically stable, asymptomatic patient with good quality of life on LVAD support presents with signs of ventricular recovery. Uncertainty remains on whether to remove the LVAD. The present study was the first to incorporate a decision analysis approach as a means of simultaneously controlling for the many factors that can affect the ultimate decision of removing or continuing LVAD support. For patients considered in the model, continued LVAD support tended to maximize the quality-adjusted life expectancy versus the decision to remove the device.

Decision analysis is an approach used to assess treatment options in situations in which no specific data from randomized trials are available (8). The use of decision analysis is appropriate when there is uncertainty about the appropriate clinical strategy for patients with a given health state. We decided to use this tool to address the explantation of a mechanical assist device in clinically stable patients with signs of ventricular recovery. The experience in this area is very limited, and only single-centre experience with a small number of patients has been published (6,7,25). Moreover, due to the limited number of patients undergoing assessment for ventricular recovery, a prospective study is not feasible. Decision analysis is a useful tool in this context.

Previous reports have shown that significant myocardial recovery after LVAD therapy occurs in a small percentage of patients with end-stage heart failure (17), most of whom have idiopathic dilated cardiomyopathy. Although complete ventricular recovery occurs in a small number of patients, it is suggested that due to the shortage of donor organs, all patients undergoing LVAD support should be systematically evaluated for evidence of myocardial recovery (2,3).

Several publications (4,6,7) have reported that in selected patients, an LVAD can be removed after demonstrating left ventricular functional improvement. However, most of these publications included patients who developed device complications, such as infection, and therefore had a clear indication for LVAD explantation. Our decision model considered only stable patients without clinical indications for LVAD explantation.

The model was sensitive to the utility after heart transplantation, indicating that patients with high utilities (higher than 0.7) should continue with LVAD support, whereas patients should be considered for LVAD explantation when the utility level is below 0.7. Therefore, if a clinically stable patient believes that a heart transplant will not provide enough clinical benefits, clinicians should carefully assess that patient for explantation. Currently, in Canada, LVADs are approved as a bridge to transplantation and not as destination therapy. Therefore, if a stable patient does not wish to receive a transplant or if complications preclude transplantation, he or she may be considered for LVAD explantation.

The model was sensitive to the probability of late complications post-LVAD. As the probability of complications increased, the strategy preference changed from 'continue' to 'remove' the LVAD. This finding is supported by several publications (7,14,15), which suggest that urgent LVAD

explantation is the preferred strategy in cases of life-threatening complications related to the device.

Limitations

Our model has several limitations. The probabilities and utilities in the model were derived after an exhaustive review of the literature. However, there are limited data available regarding the utilities of patients supported with a mechanical assist device. Some of the probabilities and utilities were based on expert judgment, and these estimates are subject to bias.

Some transition states (implantation of a second LVAD or a second heart transplant) were not incorporated into the model. Comorbidities such as diabetes, renal dysfunction or positive panel reactive antibody should be considered when determining the appropriate strategy.

CONCLUSIONS

The decision analysis suggests that with appropriate patient selection, continued LVAD support in asymptomatic patients who have signs of ventricular recovery appears to be the preferred strategy for conveying greater QALM compared with LVAD explantation. As the probability of complications after LVAD implantation increased (greater than 28%), the strategy preference changed from 'continue' to 'remove' the LVAD.

This model assessed the effectiveness of two strategies in terms of quality of life and life expectancy. Costs were not addressed in the present paper.

The greatest value of this decision analysis is in its potential as a decision making aid for patients. The model may be used to discuss the risks involved with each option and to determine the best treatment plan. This analysis may also be a useful tool for physicians to establish the most appropriate management strategy. Individual patient characteristics, including comorbidities, local expertise in performing operations (LVAD implantation or explantation and transplantation) and patient preference are important when making this difficult decision.

REFERENCES

- Delgado D, Rao V, Ross H, Verma S, Smedira NG. Mechanical circulatory assistance: State of art. *Circulation* 2002;106:2046-50.
- El-Banayosy A, Korfer R, Arusoglu L, et al. Bridging to cardiac transplantation with the Thoratec Ventricular Assist Device. *Thorac Cardiovasc Surg* 1999;47(Suppl 2):307-10.
- Zafeiridis A, Jeevanandam V, Houser S, et al. Regression of cellular hypertrophy after ventricular assist device support. *Circulation* 1998;98:656-62.
- Kumpati GS, McCarthy PM, Hoercher KJ. Left ventricular assist device as a bridge to recovery: Present status. *J Card Surg* 2001;16:294-301.
- Bruckner BA, Stetson SJ, Perez-Verdia A, et al. Regression of fibrosis and hypertrophy in failing myocardium following mechanical circulatory support. *J Heart Lung Transplant* 2001;20:457-64.
- Delgado DH, Rao V, Miriuka S, et al. Explantation of a mechanical assist device: Assessment of myocardial recovery. *J Card Surg* 2004;19:47-50.
- Khan T, Delgado RM, Radovancevic B, et al. Dobutamine stress echocardiography predicts myocardial improvement in patients supported by left ventricular assist devices (LVADs): Hemodynamic and histologic evidence of improvement before LVAD explantation. *J Heart Lung Transplant* 2003;22:137-46.
- Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Part 1 – getting started. *Med Decis Making* 1997;17:123-5.
- Naimark D, Krahn M, Naglie G, Redelmeier D, Detsky A. Primer on medical decision analysis: Part 5-working with Markov processes. *Med Decis Making* 1997;17:152-9.
- Anderson R. United States life tables, 1998. *Natl Vital Stat Rep* 2001;48:1-40.
- Liu P, Arnold M, Belenkie I, et al; Canadian Cardiovascular Society. The 2001 Canadian Cardiovascular Society consensus guideline update for the management and prevention of heart failure. *Can J Cardiol* 2001;17(Suppl E):5E-25E.
- Hunt SA, Baker DW, Chin MH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure); International Society for Heart and Lung Transplantation; Heart Failure Society of America. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001;104:2996-3007.
- Bennett LE, Keck BM, Hertz MI, Trulock EP, Taylor DO. Worldwide thoracic organ transplantation: A report from the UNOS/ISHLT international registry for thoracic organ transplantation. *Clin Transpl* 2001;25:40.
- Rose EA, Gelijns AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
- Lazar R, Shapiro P, Jaski B, 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.
- Dembitsky W, Tector A, Park S, et al. Left ventricular assist device performance with long-term circulatory support: Lessons from the REMATCH trial. *Ann Thorac Surg* 2004;78:2123-30.
- Mancini D, Benjaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. *Circulation* 1998;98:2383-9.
- Entwistle J III. Short- and long-term mechanical ventricular assistance towards myocardial recovery. *Surg Clin North Am* 2004;84:201-21.
- Moskowitz A, Weinberg A, Oz MC, Williams D. Quality of life with an implanted left ventricular assist device. *Ann Thorac Surg* 1997;64:1764-9.
- Hummel S, Piercy J, Wright R, Davie A, Bagust A, McMurray J. An economic analysis of the Survival and Ventricular Enlargement (SAVE) study. Application to the United Kingdom. *Pharmacoeconomics* 1997;12:182-92.
- Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. Preferences for quality of life or survival expressed by patients with heart failure. *J Heart Lung Transplant* 2001;20:1016-24.
- Holohan TV. Cost-effectiveness modeling of simultaneous pancreas-kidney transplantation. *Int J Technol Assess Health Care* 1996;12:416-24.
- van Hout B, Bonsel G, Habbema D, van der Maas P, de Charro F. Heart transplantation in the Netherlands; costs, effects and scenarios. *J Health Econ* 1993;12:73-93.
- Piccione W Jr. Left ventricular assist device implantation: Short and long-term surgical complications. *J Heart Lung Transplant* 2000;19:S89-94.
- Muller J, Wallukat G, Weng YG, et al. Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. *Circulation* 1997;96:542-9.
- Hetz R, Muller J, Weng Y, et al. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. *Ann Thorac Surg* 1999;68:742-9.
- Loebe M, Weng Y, Muller J, et al. Successful mechanical circulatory support for more than two years with a left ventricular assist device in a patient with dilated cardiomyopathy. *J Heart Lung Transplant* 1997;16:1176-9.