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Predicting Long Term Outcome in Patients Treated With Continuous Flow Left Ventricular Assist Device: The Penn–Columbia Risk Score

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Background—Predicting which patients are unlikely to benefit from continuous flow left ventricular assist device (LVAD) treatment is crucial for the identification of appropriate patients. Previously developed scoring systems are limited to past eras of device or restricted to specific devices. Our objective was to create a risk model for patients treated with continuous flow LVAD based on the preimplant variables.

Methods and Results—We performed a retrospective analysis of all patients implanted with a continuous flow LVAD between 2006 and 2014 at the University of Pennsylvania and included a total of 210 patients (male 78%; mean age, 56 ± 15 ; mean follow-up, 465 ± 486 days). From all plausible preoperative covariates, we performed univariate Cox regression analysis for covariates affecting the odds of 1-year survival following implantation (*P*<0.2). These variables were included in a multivariable model and dropped if significance rose above *P*=0.2. From this base model, we performed step-wise forward and backward selection for other covariates that improved power by minimizing Akaike Information Criteria while maximizing the Harrell Concordance Index. We then used Kaplan—Meier curves, the log-rank test, and Cox proportional hazard models to assess internal validity of the scoring system and its ability to stratify survival. A final optimized model was identified based on clinical and echocardiographic parameters preceding LVAD implantation. One-year mortality was significantly higher in patients with higher risk scores (hazard ratio, 1.38; *P*=0.004). This hazard ratio represents the multiplied risk of death for every increase of 1 point in the risk score. The risk score was validated in a separate patient cohort of 260 patients at Columbia University, which confirmed the prognostic utility of this risk score (*P*=0.0237).

Conclusion—We present a novel risk score and its validation for prediction of long-term survival in patients with current types of continuous flow LVAD support. (*J Am Heart Assoc.* 2018;7:e006408. DOI: 10.1161/JAHA.117.006408.)

Key Words: continuous flow • left ventricular assist device • outcome • risk score

echanical assist devices have emerged as an established therapeutic option for patients with end-stage heart failure.¹ Predicting which patients are unlikely to benefit from left ventricular assist device (LVAD) implantation is essential in order to identify appropriate patients while excluding those considered futile. The need for risk prediction before LVAD implantation has led to the recognition of various risk factors, including age, low serum albumin, low platelet count, impaired renal function, and high international normalized ratio,^{2,3} and to the development of several risk scores for short-term (90 days) mortality.^{2,3} Lietz et al² retrospectively analyzed preoperative clinical data of patients treated with pulsatile LVAD (HeartMate XVE) as destination therapy and evaluated a risk scoring system consisting of 9 risk factors for

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/7/6/e006408/DC1/embed/inline-supplementary-material-1.pdf *Dr Birati and Dr Hanff contributed equally to this work.

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Clinical Perspective

What Is New?

- Previously developed scoring systems are limited to past eras of device or restricted to specific devices, and there are currently no validated long-term risk models for this population.
- In this study, we aimed to generate a long-term risk model for patients undergoing ventricular assist device implantation.
- In this retrospective analysis, we analyzed various parameters at preimplant and created a risk model for long-term mortality.
- The risk score was then validated in a separated patient cohort at Columbia University.
- An online calculator was created for easier application of the formula (http://penncolumbiariskscore.weebly.com)

What Are the Clinical Implications?

 Our novel and simple risk model for prediction of long-term mortality based on preimplant characteristics may improve patient selection and will allow identifying high-risk patients.

estimation of 90-day mortality.³ Cowger et al generated the HeartMate II Risk Score (HMRS) for predicting LVAD candidate 90-day mortality.³ Although the HeartMate II Risk Score was originally created to predict 90-day survival, it was also found to predict risk several months after LVAD implant.³

Although the importance of risk profile is clear, there is currently no validated risk score estimating the long-term survival of continuous flow LVAD (cf-LVAD) patients. Our goal was to create a risk model predicting the long-term survival of LVAD patients based on the patients' preimplant characteristics.

Methods

Study Design

A derivation sample was selected from a single-center retrospective cohort of all 571 patients implanted with an LVAD at the Hospital of the University of Pennsylvania from 2006 to 2014. Within this cohort, we analyzed only those patients who were implanted with a cf-LVAD (n=223), which included Heartmate II (St Jude Medical Ltd, St. Paul, MN) and HVAD (HeartWare Ltd, Framingham, MA) models. We excluded all patients who were simultaneously implanted with a right ventricular assist device (n=13), leaving a final study sample of 210 patients.

A validation sample was then similarly constructed retrospectively from an independent set of 260 patients who underwent LVAD implantation at Columbia University's New York-Presbyterian Hospital from 2006 to 2013. Patients in the validation cohort were similarly excluded for simultaneous RVAD implantation and restricted to cf-LVADs.

Cumulative survival within 1 year after LVAD implantation was the primary outcome. Patients who underwent heart transplant before 1 year contributed person-time at risk up to the time of transplant, but were afterward right censored from all analyses. The institutional review board of both institutions approved the study protocol.

Subjects' informed consent was waived. The de-identified data, analytical methods, and study materials that support the findings of this study are available from the corresponding author upon reasonable request.

Statistical Analysis

The derivation data set contained data from 155 independent clinical variables (Table S1). Among these, 17 variables had a plausible influence on 1-year mortality and <25% missing data. Parameters were either continuous (eg, platelet count), ordinal (eg, level of right ventricular dysfunction), dichotomous (eg, diabetic or not diabetic), or categorical (eg, race). Body mass index (BMI) was a continuous variable treated as a spline term for BMI <20, 20 to 25, or >25. Right ventricular dysfunction, aortic insufficiency, mitral regurgitation, and tricuspid regurgitation were assessed at the University of Pennsylvania Echocardiography laboratory as absent, mild, moderate, or severe.

Each of these variables was tested for its univariate association with 1-year mortality in a Cox proportional hazard regression and was dropped from the initial model for P>0.2. Remaining variables were entered into a multivariate Cox proportional hazard model and eliminated for P>0.2. From this baseline model, we applied step-wise forward selection of any variables that improved model explanatory power based on area under the curve (AUC, assessed by Harrel's C-Index)⁴ so long as this did not deteriorate model likelihood ratio (assessed by Akaike Information Criteria [AIC]⁵ ie, compared with the baseline model before step-wise forward regression, if the AUC remained the same or worse, no increase in AIC was allowed. If the AUC improved, we tolerated an increase in the AIC by no more than 0.5%. Any further increase in AIC was considered detrimental to the model and led to exclusion of that variable). Spline terms were generated where appropriate and included if model explanatory power improved. Potential interactions were assessed between each covariate in the final multivariable model. Analysis was performed using Stata software (version 12.0; StataCorp LP, College Station, TX).

Score Generation and Survival Analysis

Each independent variable in the final model had an associated hazard ratio from the Cox proportional hazard

regression. These ratios were log transformed to a linear scale and then directly imported into a novel score that added each individual component, thereby weighting the relative importance of each contributing covariate by its hazard ratio. Patients were divided into tertiles of risk score that corresponded to a "lowest risk," "moderate risk," and "highest risk" group. Cumulative survival between these 3 groups was assessed up to 1 year after LVAD implantation using Kaplan– Meier analysis, again right censoring for any patients that were heart transplanted before the 1-year mark. Differences in the distribution of survival between the 3 tertiles were assessed with the log-rank test.

Model Validation

This novel risk score was then applied to all patients within the validation cohort at Columbia University Medical Center for an independent assessment of score performance. Model fit was assessed with the AUC, and cumulative survival distributions between tertiles of risk score were assessed with Kaplan–Meier analysis and the log-rank test.

Results

Model Derivation and Score Generation

A total of 210 patients were included in our derivation cohort who underwent implantation of a continuous flow LVAD without concurrent right ventricular assist device. One hundred eighty-two of these devices were Heartmate II (87%) and 28 were HVAD HeartWare (13%). Seventy percent of the patients were male, 48% white, and 20% black, with average age 56 at time of implant. Initial indications for LVAD were bridge to transplant (37%), bridge to decision (8%), destination therapy (52%), or bridge to recovery (3%). One-year mortality among all LVAD patients who did not undergo heart transplant was 29%. Table 1 summarizes the baseline characteristics of the study cohort at the University of Pennsylvania and the validation cohort at Columbia University Medical Center.

Exploratory analysis starting with 17 plausible covariates demonstrated 7 variables associated with mortality (P<0.2) in Cox proportional hazard models (Table 2). All 7 of these variables were then assessed for significance in a multivariate Cox proportional hazard model. Two variables, age and serum creatinine, retained significance (P<0.2) in the multivariate model and formed our base model (Table 3).

From this base model, we performed step-wise forward selection with each of the previous 17 covariates, assessing the impact of each variable on 2 measures of model explanatory power: AIC and AUC. An additional 4 variables (BMI, total serum bilirubin, right ventricular dysfunction, and aortic insufficiency) were found to improve AUC without

Table 1. Baseline Characteristics of Derivation Cohort(University of Pennsylvania) and Validation Cohort (ColombiaUniversity)

Characteristic	University of Pennsylvania (n=210)	Columbia University (n=260)	P Value
Age, mean±SD	56±15	57±14	0.89
Sex (% male)	78	81	0.42
Race, %			
White	48	62	0.002
Black	20	20	1
Other	32	18	0.26
Diabetic (% HgA1c >6.5)	47	37	0.029
VAD indication, %			
Bridge to transplant	37	69	<0.001
Destination therapy	52	27	<0.001
Bridge to decision	8	3	0.016
Bridge to recovery	3	1	0.11
Body mass index, mean \pm SD	28.0±6.7	27±5	0.74
Active tobacco smoker within 1 year, %	40	42	0.66
Hyperlipidemia, %	65	49	< 0.001
Ejection fraction, mean \pm SD	16±7	17±6	0.81

HgA1c indicates glycated hemoglobin; VAD, ventricular assist device.

detriment to AIC, and they were added to the base model. Thus, the final model included: age, serum creatinine, and total bilirubin assessed as continuous variables; BMI as a spline variable for low BMI (<20), normal BMI (20 to 25), and elevated BMI (>25); and 2 echocardiographic parameters right ventricular dysfunction and aortic insufficiency assessed as mild, moderate, or severe. The final model had an AIC of 437 and an AUC of 73%. No covariates had significant interactions with one another in the final model.

From this final multivariable model, we generated a novel score directly extracted from the model's log-transformed hazard ratios (Figure 1). This ensured that scores would be proportional to their weight in the model. An online calculator was created for easier application of the formula (http://pe nncolumbiariskscore.weebly.com). In our cohort, scores had a range of 1.8 to 10.1, mean 5.9 ± 1.35 , and median 6.0 (Figure 2). Stratified by indication, the score among patients who were bridge to transplant had range 1.7 to 8.4, mean 5.8, and median 6.0; patients who were destination therapy had range 3.3 to 10.1, mean 6.3, and median 6.3; patients who were bridge to recovery had range 2.4 to 7.3, mean 5.1, and median 5.4; and patients who were bridge to decision had range 3.3 to 6.9, mean 5.4, and median 5.5. Destination

Table 2. Univariate Association With Mortality in SeparateCox Proportional Hazard Models

Covariate	Hazard Ratio	P Value		
BMI <20	0.8	0.48		
BMI 20 to 25	1.22	0.91		
BMI >25	0.91	0.86		
Sex	1	0.99		
Age*	1.04*	<0.001*		
Type 2 diabetes mellitus	0.87	0.59		
Race				
White	1.04	0.84		
Black	0.64	0.21		
Other	1.05	0.85		
Atrial fibrillation	1.19	0.47		
Cerebrovascular accident	0.66	0.27		
Coronary artery disease*	1.64*	0.047*		
Right ventricular dysfunction	1.07	0.34		
Tricuspid regurgitation	0.94	0.38		
Mitral regurgitation*	0.9*	0.11*		
Aortic insufficiency*	1.18*	0.031*		
Ejection fraction	0.99	0.94		
Hemoglobin, g/dL*	0.87*	0.044*		
Platelet count	0.99	0.34		
Serum creatinine*	1.34*	0.005*		
Total serum bilirubin*	1.23*	0.096*		

Log rank, P=0.005. BMI indicates body mass index in kg/m². *P<0.20.

therapy patients tended to have a higher score on average, though a comparison of means across indication by ANOVA did not meet threshold for significance (P=0.052), albeit with a reduction in power for a subgroup analysis.

Table 3.Multivariate Association With Mortality in a SingleCox Proportional Hazard Models

Covariate	Hazard Ratio	P Value
Age*	1.05*	0.001*
Coronary artery disease	1.35	0.396
Mitral regurgitation	0.97	0.75
Aortic insufficiency	1.02	0.82
Hemoglobin, g/dL	1.01	0.88
Serum creatinine*	1.71*	0.003*
Total bilirubin	1.17	0.28

**P*<0.20.



Figure 1. The Penn—Columbia Risk Score. The preimplant clinical and echocardiographic parameters utilized to generate the Penn—Columbia risk score with weighted value of each variable in tabulation of risk score. The additive result generated scores below 6, thus associated with low risk and favorable 1-year survival, scores between 6 and 6.7, associated with high risk and unfavorable 1-year survival (also seen in Figure 3). For example: A 64 year old patient with creatinine level of 1.6 mg/dl and total bilirubin of 1.5 mg/dl. His BMI was 28 and he has moderate right ventricular dysfunction and mild aortic insufficiency. This patient's score is: 64*0.064+1.6*0.541+1.5*0.214+28*0.047+0.165+0.216=6.9796. BMI indicates body mass index. Creatinine in mg/dl, Total Bilirubin in mg/dl.

Survival Analysis

Figure 3 shows the cumulative survival curve using the novel risk score. Patients were divided into tertiles of risk score,



Figure 2. Distribution of the Novel Score within the patient cohort. This graph shows the distribution of the cohort patients across the risk score spectrum.



Figure 3. Twenty-four months survival distributions by tertile of risk score in the derivation cohort. Kaplan–Meier survival curve representing the survival distributions among the cohort, stratified by tertile. Log rank, p=0.005.

making a low risk (2.50–5.95), medium risk (5.96–6.74), and high risk (6.75–10.10) group. As seen in the graph, 1-year mortality was significantly increased in the highest risk group (50%) relative to the low- (21%) and medium-risk (23%) groups. The log-rank test comparing survival distributions among the 3 groups was statistically significant with P<0.001. Risk score was not associated with LVAD-associated complications occurring during the first year after implantation, such as acute right ventricular failure, LVAD thrombosis, or gastrointestinal bleeding.

Model validation

The novel risk score derived from the LVAD cohort at the University of Pennsylvania was then applied to LVAD cohort from Columbia University Medical Center. Again, mortality in the highest risk group was greater than the low- or medium-risk groups with P=0.02 by the log rank test (Figure 4).

Discussion

According to the seventh annual report of the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support),¹ the number of patients treated with continuous flow ventricular assist device continue to rise, with more than 2000 implants per year occurring in the United States alone.¹ With the increasing number of patients treated with durable assist device therapy, patient selection is essential to determine which patients will benefit from this therapy. In the current study, we generated a novel risk score, based on a combination of preimplant clinical, laboratory, and echocardiographic characteristics, identifying patients at high risk of 1-year mortality with cf-LVAD support. Importantly, our risk



Figure 4. Columbia University Medical Center survival curve divided according to the risk score. Kaplan–Meier survival curve representing the survival distributions of the validation cohort stratified by tertile. Log rank, *P*=0.02.

model was validated at Columbia University Medical Center in a similar patient cohort.

All risk scores published so far focused on the short-term survival (ie, 90-day mortality).^{2,3} The Lietz risk score² was the first risk score to predict the short-term outcomes of patients treated with first-generation, pulsatile flow, ventricular assist devices.² Given that the vast majority of the patients on LVAD support are currently being treated with second- and thirdgeneration continuous flow devices and these devices have different outcome profile compared to the first-generation devices, the Lietz's risk score should not be used in the current practice. The HeartMate II risk score used the data that were collected in the HeartMate II trial.³ It was originally planned to predict the 90-day survival of patients with HeartMate II assist device. Based on this risk score, patients were divided into 3 groups based on 90-day mortality rate: low risk with 4%, medium risk with 16%, and high risk with 29%.³ Interestingly, the differences between the groups remained significant after a year.³ Thomas et al tried to validate the HMRS in a cohort of patients treated at the Columbia University Medical Center.⁶ However, according to their findings, patient survival was similar regardless of HMRS stratification and HMRS was not valid in predicting 90-day survival in this large-volume academic center.⁶ Small cohorts validated the use of the Seattle Heart Failure model⁷ and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)⁸ as predictors of survival in LVAD candidates.

Most variables used in our risk model have been proven to be associated with poor outcomes. Atluri et al analyzed the INTERMACS national registry and divided the patients into 2 age groups (<70 and \geq 70 years). Not surprisingly, advanced age was found to be a predictor of increased mortality after cf-LVAD implantation.⁹ Age was also found to be a significant predictor both in the Lietz² as well in the HeartMate II risk scores.³ Creatinine was significant in the HeartMate II model, but not in Lietz risk score, and bilirubin was not significant in ORIGINAL RESEARCH

both studies.^{2,3} Interestingly, our model uses 2 echocardiographic parameters: right ventricular dysfunction and aortic insufficiency (Al). Al in patients supported with LVAD may lead to a circulatory loop, leading to ineffective forward flow and inadequate organ perfusion. The effect of Al on survival is not clear. Cowger et al analyzed the effect of the postimplant Al on survival of 166 patients treated with durable LVAD support.¹⁰ According to their results, postimplant development of Al did not affect survival or the risk of mitral regurgitation.¹⁰ Our study is the first to show that *preimplant* Al may affect long-term survival. Right ventricular function has been associated with increased risk of postimplant acute right ventricular failure and impaired survival.¹¹ However, no risk model in the past had used preimplant right ventricular dysfunction as a parameter.

Our risk score is the first to predict long-term outcome in patients treated both with HeartMate II and HeartWare devices. The main limitation of our model is being a retrospective single-center trial. However, validating the model in another large-volume academic center, with different patient characteristics, allows us to confidently assume that this is an accurate tool for prediction of long-term survival of this population. Moreover, our model, unlike the HeartMate II risk model, evaluates patients' not on clinical trials and represents the "real-life" management of LVAD patients. Another advantage of our risk model is in its simplicity given that it uses basic clinical and echocardiographic parameters that can be estimated by every local cardiologist. Needless to say, as a retrospective analysis it is always possible that the risk-score variables actually reflect more-proximal causes of increased risk that are not as easily measured such as duration of heart failure. However, our risk score variables are absolute and can be easily obtained for every candidate. As such, our risk score is an important bedside tool that is well validated to aid in-but not replace-clinical judgment for patients being considered for LVAD implantation. It is likely that the "PENN-COLUMBIA risk score" could be applied to the INTERMACS registry, but currently not applicable based on the variables entered. Enhanced data collection and risk assessment is desirable.

In conclusion, we present a novel and validated risk model predicting the long-term survival of LVAD patients based on patients' preimplant characteristics. Predicting which patients are at high risk may improve patients' selection on the one

Disclosures

Dr Birati received fellowship and research support by Heart-Ware Ltd and is a consultant for Luitpold Pharmaceuticals, Inc. Dr Goldberg is a consultant for Thoratec, St. Jude, and Respircardia. Dr Margulies received research grant support from Juventis Therapeutics, Celladon Corporation, Thoratec Corporation, and Merck and Co, Inc. He is also a consultant for Janssen, Merck, Pfizer, Ridgetop Research, AstraZeneca, and NovoNordisk. Dr Rame received research grant support from Thoratec Corporation and HeartWare Ltd. Drs Hanff, Maldonado, Grandin, Kennel, Mazurek, Phillips, Vorovich, Seigerman, Acker, Naka, Wald, Jessup, Atluri, and Schulze have no disclosures.

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SUPPLEMENTAL MATERIAL

Table S1. List of all Independent Clinical Variables Considered in the Derivation Dataset.

Demographics and Medical History, Pre-implantation
Sex
Race
American Society of Anesthesia (ASA) Score
Weight
Height
Body Mass Index
History of coronary artery disease
History of pulmonary hypertension
History of COPD
History of diabetes mellitus
History of smoking
History of hypertension
History of hyperlipidemia
History of carotid stenosis
History of atrial fibrillation
History of cerebrovascular accident
History of chronic renal insufficiency
History of renal failure requiring dialysis
Other important past medical history
Etiology of patient's heart failure
Reason for LVAD exchange
Patient has progressive CHF
Patient has end-stage heart failure
Patient has severe coronary artery disease
Patient has increasing shortness of breath or paroxysmal nocturnal dyspnea
Patient was transferred from an outside hospital the same admission as LVAD implantation
LVAD indication (i.e. bridge to transplant, bridge to decision, destination, or bridge to
recovery)
Duration of patient's heart failure
History of gastrointestinal bleeding
History of ventricular arrythmia
Type of Prior stroke (hemorrhagic versus ischemic)
History of venous thromboembolism
Patient is insulin dependent
INTERMACS Class at time of LVAD implantation
Patient on Beta Blocker

- Patient on ACE inhibitor or Angiotensin Receptor Blocker
- Patient on aldosterone antagonist
- Patient on nitrates
- Patient on hydralazine
- Patient on digoxin
- Patient on diuretic
- Patient on vasopressor
- Patient on an antiarrhythmic medication
- Patient taking an oral pulmonary vasodilator
- Patient on aspirin
- Patient on other anti-platlet agents
- Patient on anticoagulation
- QRS duration on pre-LVAD ECG
- Implantable cardioverter defibillator present
- Pacemaker present
- Biventricular pacemaker present

Echocardiographic Variables, Pre-Implantation

- Echo date
- Degree of right ventricular dysfunction Degree of tricuspid regurgitation Degree of mitral regurgitation Degree of aortic insufficiency LV ejection fraction Patent foramen ovale present Left ventricular end-diastolic diameter LV end-systolic diameter Left atrial diameter from parasternal long axis Left atrial size (qualitative) Right ventricular systolic pressure Estimated right atrial pressure Estimated pulmonary arterial systolic pressure (PASP) Tricuspid annular planar systolic excursion (TAPSE) Interventricular septal flattening Interventricular septal position

Hemodynamics, Pre-implantation

Date of hemodynamic measurements

Heart rate Systolic blood pressure Diastolic blood pressure Mean arterial blood pressure Central venous pressure Pulmonary artery systolic pressure Pulmonary artery diastolic pressure Mean pulmonary arterial pressure Cardiac output Cardiac index Pulmonary artery oxygen saturation (SvO2) Stroke volume index Right ventricular stroke work index Patient on milrinone at time of measurement Patient taking oral sildenafil Patient receiving inhaled prostacyclin

Laboratory Values, Pre-implantation

White blood cell count Hemoglobin Platelets Blood urea nitrogen Creatinine Sodium Potassium Carbon Dioxide Aspartate triaminase (AST) Alamine triaminase (ALT) Total bilirubin Sodium Bicarbonate Lactic acid Albumin Prealbumin INR PTT Lactate Dehydrogenase Plasma free hemoglobin Haptoglobin Hemoglobin A1c

Implantation Variables

- LVAD implantation date
- Age at implant
- LVAD, RVAD, BiVAD, or total artificial heart implanted
- LVAD model
- Did patient undergo LVAD exchange
- Did patient receive a delayed RVAD
- Number of days between LVAD and RVAD
- Type of RVAD
- Intubation required pre-operatively
- ECMO required pre-operatively
- Intra-aortic balloon pump required pre-operatively
- Inotropes required pre-operatively
- CABG performed intra-operatively
- Tricuspid valve repair performed intra-operatively
- Mitral valve repair performed intra-operatively
- Aortic valve closure performed intra-operatively
- Aortic valve repair performed intra-operatively
- Aortic valve replacement performed intra-operatively
- Cardiopulmonary Bypass time
- Cross Clamp time
- Surgical approach
- Prior sternotomy present
- Post-implant cryoablation
- Factor 7 given intra-operatively
- Units of fresh-frozen plasma given intra-operatively
- Units of packed red blood cells given intra-operatively
- Units of platelets given intra-operatively
- Time to extubation
- ICU length of stay
- Milrinone present immediately post-operatively
- Date milrinone started
- Dose of milrinone post-operatively
- Date milrinone stopped
- Neosynephrine present immediately post-operatively
- Date neosynephrine started
- Dose of neosynephrine
- Date neosynephrine stopped

- Vasopressin present immediately post-operatively
- Date vasopressin started
- Dose of vasopressin
- Date vasopressin stopped
- Levophed present immediately post-operatively
- Date levophed started
- Dose of levophed
- Date levophed stopped
- Epinephrine present immediately post-operatively
- Date epinephrine started
- Dose of epinephrine
- Date epinephrine stopped