hearts

MDPI

Article

Is Greater Than 0.5 MAC Inhalational Agent Use Post-Bypass Related to Need for Inotropic and/or Vasoconstrictor Support?

Tara A. Lenk [1,2,*], Carlos E. Guerra-Londono [1], Thomas E. Graul [1], Marc A. Murinson [1], Prabhdeep K. Hehar [1], George Divine [1] and Raj K. Modak [1]

[1] Anesthesiology Department, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA; cguerra1@hfhs.org (C.E.G.-L.); tgraul1@hfhs.org (T.E.G.); mmurins1@hfhs.org (M.A.M.); phehar@hfhs.org (P.K.H.); gdivine1@hfhs.org (G.D.); rajmodak@umich.edu (R.K.M.)
[2] Anesthesiology, Mission Hospital, 509 Biltmore Ave, Asheville, NC 28801, USA
* Correspondence: tara.ann.s@gmail.com

Abstract: Background and Aims: We hypothesized that maintaining a patient on moderate–high doses of potent inhalational agent for greater than 30 min during the post-bypass period would be an independent predictor of initiation and usage of either inotropic and/or vasopressor infusions. Setting and Design: This study is a retrospective design and approved by the institutional review board. The setting was a single-center, academic tertiary care hospital in Detroit, Michigan. Materials and Methods: Three-hundred, ninety-seven elective cardiac surgery patients were identified for chart review. Electronic medical records were reviewed to collect demographics and perioperative data. Statistics used include a propensity score regression adjusted analysis utilizing logistic regression models and a multivariable model. Results: A propensity score regression adjusted analysis was performed and then applied in both univariate and multivariate logistic regression models with a p value of <0.05 reaching statistical significance. Fifty-six percent of the participants had an exposure of greater than 30 min of a minimum alveolar concentration of isoflurane greater than 0.5 ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$) in the post-bypass period. After adjusting for propensity score, this was found to be a significant predictor of inotrope and/or vasoconstrictor use post-bypass (OR 2.49, 95% CI 1.15–5.38, $p = 0.021$). In the multivariate model, pulmonary hypertension (OR 5.9; 95% CI 1.33–26.28; $p = 0.02$), Euroscore II (2.73; 95% CI 1.35–5.5; $p = 0.005$), and cardiopulmonary bypass hours (OR 1.86; 95% CI 1.02–3.4; $p = 0.042$) emerged as significant. Conclusions: This study showed that an $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ exposure during the immediate post-bypass period during elective cardiac surgery was an independent predictor of a patient being started on inotrope or vasoconstrictor infusions. Further research should consider a prospective design and examine depth of anesthesia during the post-bypass period.

Keywords: inhalational agent; minimum alveolar concentration; inotrope; vasopressor; perioperative morbidity; cardiac anesthesiology; ischemic preconditioning; cardioprotection

Citation: Lenk, T.A.; Guerra-Londono, C.E.; Graul, T.E.; Murinson, M.A.; Hehar, P.K.; Divine, G.; Modak, R.K. Is Greater Than 0.5 MAC Inhalational Agent Use Post-Bypass Related to Need for Inotropic and/or Vasoconstrictor Support? *Hearts* **2021**, *2*, 213–223. https://doi.org/10.3390/hearts2020017

Academic Editors: Matthias Thielmann and Kei Hayashida

Received: 21 January 2021
Accepted: 6 April 2021
Published: 13 April 2021

1. Introduction

Currently available inotropes and vasoconstrictors are a mainstay during cardiac surgery, allowing the anesthesia team to achieve adequate vascular tone and management of low cardiac output states. However, their use has been associated with excess morbidity in cardiac surgery, possibly due to the detrimental side effects of increased myocardial oxygen consumption and demand resulting from tachycardia, increased contractility and systemic vascular resistance [1]. In addition, systemic vasoconstriction can lead to reduced end-organ perfusion. If possible, inotrope and vasoconstrictor use should be avoided to limit the undesirable side effects of these drugs. A study by Fellahi et al. [2] showed an increased morbidity with the use of Dobutamine during cardiac surgery, and Fleming et al. [3] associated Milrinone with an increased risk of atrial fibrillation. A more recent propensity-matched study demonstrated increased morbidity and mortality with

higher doses of inotropic agents [4]. This suggests that unnecessary administration of these medications should be avoided. Volatile inhalational agents, despite their beneficial effects on preconditioning [5,6], may lead to excessive cardiac depression during the vulnerable post-cardiopulmonary bypass period due to their known decreases in myocardial contractility [7,8], and can lead to use of these potentially deleterious inotropic and vasopressor drugs.

Although volatiles are extremely common in contemporary cardiac anesthesiology management, the dose of volatile agents may be maintained too high in the critical post-bypass time period to achieve optimal decreases in perioperative morbidity. Hettrick et al. [9] showed that higher doses of inhaled anesthetic in barbiturate-anesthetized canines resulted in the loss of left ventricular (LV)–arterial tree coupling and decreased overall cardiac performance. Therefore, the present study aimed to examine the relationship between the exposure of post-bypass inhalational agent and the initiation of inotropic and/or vasopressor support during the same time period. We hypothesized that patients exposed to more than 0.5 minimum alveolar concentration (MAC) of potent inhalational agents for greater than 30 min ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$) during the post-bypass period would be a statistically independent predictor of the initiation and usage of either inotropic and/or vasopressor infusions.

2. Methods

2.1. Setting and Study Population

This retrospective study was conducted at an academic tertiary care hospital in Detroit, Michigan, USA. It was approved by the institutional review board and conducted in accordance with the Health Insurance Portability and Accountability Act. We accessed the electronic medical records to identify patients who underwent elective coronary artery bypass graft (CABG) surgery, valve replacement/repair, and/or aortic procedures between January 2011 and September 2015. Unique identifiers were randomly assigned to each patient, and the records were examined until a predetermined sample of 400 patient records matching the inclusion criteria was met. Only electronic medical and anesthetic records were used for the study. Patients who underwent heart transplant, placement of a ventricular-assist device, trans-catheter valve replacement in the absence of cardiopulmonary bypass (CPB), emergency procedures and those with active infection were excluded.

2.2. Study Variables and Endpoints

We collected demographic data and preoperative characteristics including age, sex, weight, body mass index, American Society of Anesthesiologists (ASA) status, surgeon, anesthesiologist, and comorbidities necessary to calculate a Euroscore II risk score for each patient.

The type of surgery was classified according to the interventions performed. As such, patients were assigned to one of 7 groups depending on if they underwent CABG only, combined CABG plus valve, only mitral valve, only aortic valve, valve (other), thoracic aorta procedure only, and thoracic aorta plus valve or CABG. Other intraoperative characteristics were the presence or absence of inotropes and/or vasopressors prior to bypass, total bypass and weaning time (from time aortic cross clamp removed to cessation of CPB), intraoperative dose of every specific inotrope or vasopressor, and the presence of a paced heart rhythm after weaning. Specifics on volume status were not recorded due to retrospective nature of data collection and difficulty collecting this information from the chart. Total aortic cross clamp and specific hemodynamic values before and after bypass were also not recorded. The inotropes and vasoconstrictors included in the analysis were Epinephrine, Dopamine, Dobutamine, Milrinone, Norepinephrine, Vasopressin, and Phenylephrine.

The weaning time period was defined as the moment the aortic clamp was removed until completion of bypass. During bypass, hemodynamic data and arterial blood gases closest to weaning period and the doses of inhaled anesthetics were collected. Additional intravenous hypnotic anesthetic agents during the case were not recorded (i.e., propofol,

benzodiazepines or opioids) due to sporadic and culturally infrequent use by the cardiac anesthetic team. The length of intensive care unit (ICU) and hospital stay, time to extubation, and postoperative laboratory data up to 72 h including serum lactate, arterial blood gases, and renal function were recorded.

2.3. Exposure

Exposure is defined and used as the cumulative minutes spent with an isoflurane concentration above 0.5 MAC (age-adjusted end-tidal concentration using MAC notation) during the time period of weaning plus post-bypass for thirty minutes or more, and is abbreviated by ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$). The exposure criteria was chosen by the research team based on clinical experience of what amount of MAC exposure significantly affects hemodynamics in cardiac surgery patients during the post-bypass period. This specific time span and MAC exposure is not based on prior literature, but rather anecdotal and clinical experience. In this study, isoflurane was the potent inhalational agent used most often during the cardiopulmonary bypass run and immediate post-bypass period in the majority of patients, as other inhalational agents are not commonly used at our institution during cardiac surgery.

2.4. Statistical Analyses

The sample size requirement was calculated to give 85% power to detect a difference in the rate of inotrope usage of 85% vs. 70% for those with and without an $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$. Assuming a ratio of 3:1 for such exposure, the total sample size required was 400 (i.e., 300 with and 100 without) was calculated. A ratio of 3:1 was chosen due to the institutional and clinical experience of the research team.

Our study employed a propensity score regression adjusted analysis. Patients were classified into those receiving $ET_{ISO} < 0.5_{MAC}$, 30 $_{min}$ vs. $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ during weaning of cardiopulmonary bypass and in the post-bypass period. Initially, a multivariable logistic regression model was developed to determine those variables associated with a propensity to receive a higher dose of inhaled anesthetic for more than 30 min. Subsequently, the propensity score was used to adjust for likelihood an exposure of $ET_{ISO} > 0.5_{MAC}$, 30 $_{min}$ or higher in logistic regression models used to assess the association of inotropic and vasopressor medications and moderate or higher dose isoflurane exposure itself, adjusting for the propensity score/probability. Variables for a multivariable model were picked using forward variable selection, after the propensity score and the indicator for exposure of $ET_{ISO} > 0.5_{MAC}$, 30 $_{min}$ were forced to be included in the model. Note: consistent with the basic rationale for a propensity adjusted analysis, the propensity score and the indicator for moderate or higher dose isoflurane exposure were retained in all the multivariable models, regardless of whether or not they were statistically significant.

3. Results

A total of 397 patients were identified and included in the data analyses. The mean age was 65 years, and 71% were male. Of the operations, 53% were CABG, with the remainder a mix of CABG plus valve, valve only, and elective thoracic procedures. Ejection fraction was on average 54%. A total of 29% had diabetes treated with insulin, 84% had a history of hypertension, 16% had a myocardial infarction in the previous 90 days, and the average Euroscore II was 2.81. Valve disease was moderate to severe in 47%, and the mean time on bypass was 2.84 h (Table 1). When stratified by any usage of vasopressors and inotropes after CPB (365 patients vs. 32 patients), statistically significant differences occurred in ICU stay (5.5 days vs. 3 days, $p = 0.006$), total length of stay (11.3 days vs. 6.8 days, $p \leq 0.001$), and time to extubation (21 h vs. 7.6 h, $p \leq 0.001$) (Table 2). For those who had inotrope and vasoconstrictors started in the ICU, infusion continued postoperatively on average for 50 h. The most common infusions started post-bypass were Epinephrine and Vasopressin. The median highest recorded dose of intraoperative epinephrine infusion was 0.03 mcg/kg/min (standard deviation (SD) of 0.03) and median total intraoperative

micrograms given were 236 (SD 376 mcg). The median hours an epinephrine infusion remained running in the ICU was 9 h (SD 20 h). The median highest recorded dose of intraoperative vasopressin infusion was 2 units/hr (SD of 2.25 units) and median total intraoperative units given were 2.27 units (SD 9.95 units). The median hours an vasopressin infusion remained running in the ICU was 10 h (SD 29 h).

There were five independent variables that were statistically significant in predicting if a patient was maintained on $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ or $ET_{ISO} < 0.5_{MAC}$, 30 $_{min}$ (Table 3). In general, patients exposed to moderate or higher exposure of isoflurane had statistically significant association with more extracardiac arteriopathy (defined as claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, or previous vascular intervention), higher Euroscore II, less Chronic Obstructive Pulmonary Disease (COPD), were younger and had lower ASA scores. A propensity score was then calculated from these five variables.

This propensity score was then used in separate logistic regression models, one for each variable of interest, to yield propensity score adjusted estimates for each variable's association with inotrope and vasopressor use (Table 4). An exposure of $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ post-bypass was found to have a statistically significant association with being started on an inotrope or vasoconstrictor post-bypass (OR 2.49, 95% CI 1.15–5.38, $p = 0.021$), after adjusting for the MAC 0.5 propensity score. A few other variables emerged as statistically significant associations with use of an inotrope or vasoconstrictor after adjustment for an $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ exposure and its propensity score. Any pulmonary hypertension (pulmonary artery systolic pressure above 30 mm Hg) was associated with more inotrope use (OR 9.90 95% CI 2.3–42.29). Moderate–severe valve disease was also a positive predictor (OR 3.65, 95% CI 1.51–8.8). Male sex was associated with being started on less inotropes/vasoconstrictors (OR 0.33 95% CI 0.11–0.96, $p = 0.042$). Combined CABG and valve surgery were associated with more inotropes/vasoconstrictor infusions than CABG alone, valve alone, or thoracic alone (OR 14.8 95% CI 1.96–111.5, $p = 0.009$). Those who had infusions started post-bypass also had had statistically longer cardiopulmonary bypass times (OR 2.56 95% CI 1.52–4.32, $p = 0.001$). However, after propensity adjustment, patients did not have a higher incidence of new atrial fibrillation or new acute kidney injury postoperatively. In the multivariable model (Table 5), duration of cardiopulmonary bypass, pulmonary hypertension, Euroscore II and $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$, were all also associated with greater inotrope or vasopressor use.

Table 1. Baseline Characteristics and Postoperative Events with Distinction of the Inhaled Anesthetic Dose during the Post-Bypass Period.

Variable Name	All (N = 397)	$ET_{ISO} < 0.5_{MAC}$, 30 min (N = 171)	$ET_{ISO} \geq 0.5_{MAC}$, 30 min (N = 226)	p-Value
Baseline Characteristics				
Age (mean ± SD)	64.85 ± 10.91	66.04 ± 9.70	63.96 ± 11.69	0.054
Male sex	282 (71%)	125 (73%)	157 (69%)	0.430
BMI (mean ± SD)	29.49 ± 7.14	29.64 ± 8.67	29.37 ± 5.75	0.728
ASA 4	353 (89%)	158 (92%)	195 (87%)	0.069
Type of Surgery				
CABG only	209 (53%)	92 (54%)	117 (52%)	0.754
Combined CABG plus valve	97 (24%)	44 (26%)	53 (23%)	
Valve	63 (16%)	25 (15%)	38 (17%)	
Thoracic Aorta	28 (7%)	10 (6%)	18 (8%)	
Creatinine Clearance (Mean ± SD)	87.13 ± 40.75	89.11 ± 37.39	85.63 ± 43.13	0.392
Pulmonary Hypertension				
None	254 (64%)	109 (64%)	145 (64%)	0.828
Moderate (PA Systolic 31–55 mmHg)	125 (31%)	53 (31%)	72 (32%)	
Severe (PA Systolic > 55 mmHg)	18 (5%)	9 (5%)	9 (4%)	
Extracardiac Arteriopathy	28 (7%)	7 (4%)	21 (9%)	0.045
Poor Mobility	3 (1%)	0 (0%)	3 (1%)	0.130
COPD	38 (10%)	23 (13%)	15 (7%)	0.022
Active Endocarditis	5 (1%)	1 (1%)	4 (2%)	0.294
Critical Preoperative State	7 (2%)	1 (1%)	6 (3%)	0.121
Previous Cardiac Surgery	22 (6%)	10 (6%)	12 (5%)	0.816
Class 4 Angina	21 (5%)	10 (6%)	11 (5%)	0.666
MI within 90 days	62 (16%)	23 (13%)	39 (17%)	0.301
Ejection Fraction % (mean ± SD)	54.42 ± 11.74	55.23 ± 11.48	53.81 ± 11.92	0.232
Diabetes on Insulin	115 (29%)	43 (25%)	72 (32%)	0.144
Hypertension	332 (84%)	144 (84%)	188 (83%)	0.785
Stroke	19 (5%)	8 (5%)	11 (5%)	0.930
Euroscore II (mean ± SD)	2.81 ± 3.37	2.35 ± 2.55	3.16 ± 3.85	0.013
Coronary Artery Disease	320 (81%)	142 (83%)	178 (79%)	0.286
Moderate or Severe Valve Disease	188 (47%)	77 (45%)	111 (49%)	0.419
History of Smoking	225 (57%)	96 (56%)	129 (57%)	0.852
Vasopressor Pre-Bypass	115 (29%)	43 (25%)	72 (32%)	0.144
CPB time in hours (mean ± SD)	2.84 ± 1.21	2.74 ± 1.08	2.92 ± 1.29	0.122
Postoperative Events				
Acute Kidney Injury	106 (27%)	50 (29%)	56 (25%)	0.320
ICU days (mean ± SD)	140 (35%)	56 (33%)	84 (37%)	0.361
Acute Kidney Injury	5.26 ± 6.90	5.04 ± 7.84	5.42 ± 6.11	0.446
Hospital Stay (mean ± SD)	10.96 ± 10.56	10.16 ± 8.46	11.56 ± 11.89	0.202

Abbreviations: $ET_{ISO} < 0.5_{MAC}$, 30_{min}: Volatile Exposure, End-Tidal Isoflurane less than 0.5 MAC for 30 min. $ET_{ISO} \geq 0.5_{MAC}$, 30_{min}: Volatile Exposure, End-Tidal Isoflurane greater than or equal to 0.5 MAC for 30 min. MAC: Minimum Alveolar Concentration BMI: Body Mass Index. ASA: American Society of Anesthesiologists Classification. CABG: Coronary Artery Bypass Graft. SD: Standard Deviation. COPD: Chronic Obstructive Pulmonary Disease. MI: Myocardial Infarction. CPB: Cardiopulmonary Bypass. ICU: Intensive Care Unit.

Table 2. Baseline Characteristics and Postoperative Events with Distinction by the Use of Inotrope and/or Vasopressor during the Post-Bypass Period.

Variable	All (*N* = 397)	Inotrope or Vasopressor USED (*N* = 32)	Inotrope or Vasopressor NOT USED (*N* = 365)	*p*-Value
Baseline Characteristics				
Volatile Exposure ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$)	226 (57%)	12 (38%)	214 (59%)	0.021
Age (mean ± SD)	64.85 ± 10.91	60.28 ± 10.57	65.25 ± 10.86	0.013
Male sex	282 (71%)	28 (88%)	254 (70%)	0.032
BMI (mean ± SD)	29.49 ± 7.14	28.62 ± 4.30	29.56 ± 7.34	0.272
ASA 4	353 (89%)	28 (88%)	325 (89%)	0.756
Type of Surgery				
CABG only	209 (53%)	26 81%)	183 (50%)	0.005
Combined CABG plus valve	97 (24%)	1 (3%)	96 (26%)	
Valve	63 (16%)	3 (9%)	60 (16%)	
Thoracic Aorta	28 (7%)	2 (6%)	26 (7%)	
Pulmonary Hypertension				
None	254 (64%)	30 (94%)	224 (61%)	0.001
Moderate (PA Systolic 31–55 mgHg)	125 (31%)	2 (6%)	123 (34%)	
Severe (PA Systolic > 55 mmHg)	18 (5%)	0 (0%)	18 (5%)	
Creatinine Clearance (Mean ± SD)	87.13 ± 40.75	107.89 ± 41.40	85.31 ± 40.24	0.003
Extracardiac Arteriopathy	28 (7%)	1 (3%)	27 (7%)	0.365
Poor Mobility	3 (1%)	0 (0%)	3 (1%)	0.607
COPD	38 (10%)	1 (3%)	37 (10%)	0.196
Active Endocarditis	5 (1%)	0 (0%)	5 (1%)	0.505
Critical Preoperative State	7 (2%)	0 (0%)	7 (2%)	0.429
Previous Cardiac Surgery	22 (6%)	0 (0%)	22 (6%)	0.153
Class 4 Angina	21 (5%)	3 (9%)	18 (5%)	0.282
MI within 90 days	62 (16%)	4 (13%)	58 (16%)	0.612
Ejection Fraction % (mean ± SD)	54.42 ± 11.74	55.44 ± 11.51	54.33 ± 11.77	0.609
Diabetes on Insulin	115 (29%)	5 (16%)	110 (30%)	0.083
Hypertension	332 (84%)	27 (84%)	305 (84%)	0.905
Stroke	19 (5%)	1 (3%)	18 (5%)	0.646
Euroscore II (mean ± SD)	2.81 ± 3.37	1.04 ± 0.56	2.97 ± 3.47	<0.001
Coronary Artery Disease	320 (81%)	26 (81%)	294 (81%)	0.923
Moderate or Severe Valve Disease	188 (47%)	7 (22%)	181 (50%)	0.003
History of Smoking	225 (57%)	14 (44%)	211 (58%)	0.124
Vasopressor Pre-Bypass	115 (29%)	5 (16%)	110 (30%)	0.083
CPB time in hours (mean ± SD)	2.84 ± 1.21	2.11 ± 0.65	2.91 ± 1.22	<0.001
Postoperative Events				
Atrial Fibrillation	106 (27%)	4 (13%)	102 (28%)	0.058
Acute Kidney Injury	140 (35%)	7 (22%)	133 (36%)	0.098
ICU days (mean ± SD)	5.26 ± 6.90	3.03 ± 0.97	5.45 ± 7.16	0.006
Hospital Stay (mean ± SD)	10.96 ± 10.56	6.88 ± 2.46	11.32 ± 10.92	<0.001
Time to extubation in hours (mean ± SD)	20.38 ± 48.97	7.62 ± 7.35	21.50 ± 50.88	<0.001
Duration of vasopressor support in ICU in hours (mean ± SD)	46.65 ± 85.18	0.00 ± 0.00	50.74 ± 87.66	<0.001

Abbreviations: $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$: Volatile Exposure, End-Tidal Isoflurane greater than or equal to 0.5 MAC for 30 min. MAC: Minimum Alveolar Concentration BMI: Body Mass Index. ASA: American Society of Anesthesiologists Classification. CABG: Coronary Artery Bypass Graft. SD: Standard Deviation. COPD: Chronic Obstructive Pulmonary Disease. MI: Myocardial Infarction. CPB: Cardiopulmonary Bypass. ICU: Intensive Care Unit.

Table 3. Multivariable Logistic Regression Model Estimates for Volatile Exposure ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$) during the Post-Bypass Period.

Variable/Category	Odds Ratio (95% C.I.)	*p*-Value
Age (per decade)	0.77 (0.63, 0.95)	0.016
ASA Physical Status (4 vs. 3)	0.47 (0.23, 0.94)	0.033
Euroscore II (per 1 unit)	1.10 (1.02, 1.20)	0.015
COPD (Yes vs. No)	0.40 (0.19, 0.81)	0.011
Extracardiac Arteriopathy (Yes vs. No)	2.40 (0.97, 5.95)	0.059

Abbreviations: $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$: Volatile Exposure, End-Tidal Isoflurane greater than or equal to 0.5 MAC for 30 min.MAC: Minimum Alveolar Concentration. ASA: American Society of Anesthesiologists. COPD: Chronic Obstructive Pulmonary Disease. C.I: Confidence Interval.

Table 4. Univariate Logistic Regression Models for Inotrope Use—Adjusted for Volatile Exposure ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$) and Calculated Propensity Score.

Variable	Odds Ratio (95% C.I.)	*p*-Value
Volatile Exposure ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$)	2.49 (1.15, 5.38)	0.021
Age (decades)	1.59 (1.13, 2.24)	0.008
Sex (Male vs. Female)	0.33 (0.11, 0.96)	0.042
Surgery: Combined CABG plus Valve	14.80 (1.96, 111.5)	0.009
Moderate to Severe Valve Disease	3.65 (1.51, 8.79)	0.004
Pulmonary Hypertension	9.90 (2.32, 42.29)	0.002
Creatinine Clearance	0.99 (0.98, 1.00)	0.003
CPB time (hours)	2.56 (1.52, 4.32)	<0.001
Surgery: Thoracic Aorta	1.91 (0.41, 8.87)	0.410
Surgery: Valve	2.94 (0.85, 10.21)	0.090
Class 4 Angina	0.53 (0.15, 1.95)	0.341
Extracardiac Arteriopathy	2.84 (0.34, 24.10)	0.338
COPD	4.50 (0.53, 38.37)	0.169
ASA (4 vs. 3)	1.24 (0.37, 4.20)	0.731
Ejection Fraction	0.99 (0.96, 1.03)	0.651
Diabetes Mellitus on Insulin	2.25 (0.84, 6.05)	0.107
Hypertension	0.93 (0.34, 2.54)	0.892
Stroke	1.81 (0.22, 14.59)	0.579
Vasopressor Pre-Bypass	2.16 (0.81, 5.79)	0.126

Abbreviations: $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$: Volatile Exposure, End-Tidal Isoflurane greater than or equal to 0.5 MAC for 30 min. ASA: American Society of Anesthesiologists. CABG: Coronary Artery Bypass Graft. COPD: Chronic Obstructive Pulmonary Disease. CPB: Cardiopulmonary Bypass. MAC: Minimum Alveolar Concentration.

Table 5. Multivariate Logistic Regression Model for the Use of Inotropic/Vasopressor Medications in the Post-Bypass Period.

Variable	Odd Ratio (95% C.I)	*p*-Value
CPB time (hours)	1.86 (1.02, 3.40)	0.042
Pulmonary Hypertension	5.90 (1.33, 26.28)	0.020
Euroscore II	2.73 (1.35, 5.50)	0.005
Volatile Exposure ($ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$)	2.57 (1.15, 5.76)	0.021

Abbreviations: $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$: Volatile Exposure, End-Tidal Isoflurane greater than or equal to 0.5 MAC for 30 min. CPB: Cardiopulmonary Bypass. MAC: Minimum Alveolar Concentration.

4. Discussion

4.1. Principal Findings

This retrospective study showed that a cumulative exposure of $ET_{ISO} \geq 0.5_{MAC}$, 30 $_{min}$ (age-adjusted, end-tidal) during the weaning and post-CPB period in elective cardiac surgery was an independent predictor of the use of inotropic or vasoconstrictor medications during the post-bypass period. This relationship remained significant even after using a propensity score to adjust for the five most confounding variables (age, ASA status, extracardiac arteriopathy, COPD, and Euroscore II) that led to more inhaled anesthetic usage. Given the documented negative effects of inotropic agents on postoperative morbidity,

lower doses of isoflurane during cardiac surgery may lead to improved patient outcomes. It is possible that the deleterious morbidity associated with inotrope and vasoconstrictor use could be partially avoided by decreasing the use of inhalational agents and utilizing other anesthetic agents for hypnosis during the post-bypass period. Our study also suggests clinically meaningful lower ICU stays, total length of stay and times to extubation. Pulmonary hypertension, Euroscore II risk score, and longer bypass time were also significantly and independently associated with more inotrope/vasoconstrictor infusions.

4.2. Other Literature

Most recently in 2013, Nielsen et al. [1] showed through propensity matching in a large sample of 2097 patients that those exposed to inotropes intraoperatively had a higher mortality, as well as more perioperative myocardial infarction, stroke, arrhythmia, and renal replacement therapy. Shahin et al. [4] studied 1326 cardiac surgery patients and found that postoperative inotrope exposure was independently associated with increased mortality and renal dysfunction. In retrospective studies, Milrinone was found to increase postoperative atrial fibrillation, and Dobutamine was found overall to increase cardiac morbidity [2].

Evidence of decreased myocardial performance caused by Isoflurane was originally published in 1971. Stevens et al. [7] found that LV stroke work was at 60% of control with 1 MAC of Isoflurane, and stroke volume was at 85% of normal at 1 MAC in 23-year-old healthy volunteers. Although these patients did not have surgical stimulation with resultant catecholamine release which would improve inotropy in young healthy patients, vulnerable hearts post-bypass may not respond quite as strongly to endogenous catecholamines and thus still display the drop in inotropy seen in this study. In 1981, Merin et al. [10] showed that Isoflurane caused cardiac depression in dog hearts, and that they were more preload-dependent suggesting cardiac depression especially at high Isoflurane concentrations. A 1995 study confirmed the work by Stevens et al. and further showed that Isoflurane decreased cardiac index from 4 to 3 L/min/m^2 at 1 MAC of isoflurane [11]. Most recently, Hettrick et al. [9] showed that above 0.9 MAC of Isoflurane, the matching of mechanical energy between LV and arterial tree deteriorates more, and there is a reduction in overall cardiac function. Most of these studies used healthy volunteers or healthy animal hearts, and therefore diseased hearts may respond very differently to the same or even lower levels of inhaled anesthetic and would be more susceptible to the effects of Isoflurane. This postulation is what determined our cutoff of 0.5 MAC post-bypass, as we thought that above 0.5 MAC would most likely impair diseased hearts at baseline especially following the myocardial tissue insults related to cardioplegia and cardiopulmonary bypass time.

Interest has been increasing in the use of inhaled agents during cardiac procedures due to the beneficial effects of ischemic preconditioning and decreased reperfusion injury. Much of the evidence supporting ischemic preconditioning was found in the experimental setting. Although an exciting prospect, these beneficial effects have not been consistent in the clinical setting [12]. For example, a study with 72 patients showed that Sevoflurane 4% given just before aortic cross-clamping had less evidence of lower biochemical markers of ischemic injury; however, the clinical incidence of myocardial injury was not different between groups [13]. A study with 40 patients that looked specifically at Isoflurane preconditioning of 1.5% end-tidal concentration immediately before cardiopulmonary bypass and the effect on myocardial performance found that LV stroke work and ejection fraction remained the same in the experimental and control groups 5 days post-surgery, although those with a left ventricular ejection fraction <50% had lower release of troponin and CKMB [14].

Although the clinical effects of high amounts of inhaled agent immediately pre-bypass is of questionable benefit clinically, some studies reported a beneficial effect on overall myocardial function from inhaled agents. A study of 49 patients found that 1 MAC of Isoflurane administration pre-bypass correlated with a higher cardiac index (2.3 L/min/m^2 pre-bypass to 3 L/min/m^2 post-bypass) 5 min after weaning from CPB in the Isoflurane-

treated group [15]. An older study in 1988 assessed improvement of overall myocardial function following volatile exposure in dog hearts and found that exposure to Isoflurane before coronary artery occlusion versus no anesthetic showed sooner return to baseline cardiac function by 5 h, whereas controls still had 50% decrease in myocardial function at the same time point [16].

Due to these beneficial effects on overall myocardial function, several studies compared total intravenous anesthesia versus inhalational anesthesia for the entirety of a cardiac procedure. De Hert et al. [17] assessed 20 patients with a baseline cardiac index of 5 L/min/m^2 who had propofol vs. sevoflurane anesthetic and found that the sevoflurane group had a smaller drop in cardiac index post-bypass (5.6 vs. 4.5 L/min/m^2), as well as needing less inotropes and vasoconstrictors. The same group looked at a sicker cohort with a baseline cardiac index of 2.3 L/min/m^2, adding a desflurane group, and found that post-bypass the propofol group had a cardiac index of 2 L/min/m^2 vs. 2.5 and 2.7 in the desflurane and sevoflurane groups [17]. A meta-analysis from 2017 recently looked at this question and reported good-quality evidence that sevoflurane is more effective than propofol in decreasing rates of death in on-pump CABG; however, overall the quality of evidence comparing intravenous anesthetics to inhalational anesthetics in cardiac surgery was insufficient to draw firm conclusions [6]. Finally, a recent large multi-center randomized controlled trial by Landoni et al. [18] studied if volatile anesthetics vs. total intravenous anesthesia changed mortality at 1 year postoperatively and was stopped for futility early due to no significant difference between groups.

Thus, some evidence from smaller clinical studies have shown that volatiles can help preserve myocardial function when used throughout the whole procedure in both healthy patients with normal preoperative ejection fractions and sicker patients with lower preoperative ejection fractions through decreasing oxygen consumption and indirectly protecting the heart in this manner. However, this protective effect was not seen when studied in a randomized, multicenter model. Volatiles may be a good option with similar outcomes to total intravenous anesthesia until the concentration is too high, especially in a vulnerable time when potentially deleterious inotrope and vasoconstrictors are started to promote forward flow. Our results suggest that higher doses of volatile agents during the critical post-bypass and weaning periods can potentially depress the heart function to a degree where inotropes and vasoconstrictors are started unnecessarily. Until further clinical studies clarify the role of ischemic preconditioning and cardioprotection from volatile agents, it is important to reconsider the association between higher doses of volatile agents and the need for inotropes and vasoconstrictors. Our results show that it may be wise to avoid use of higher than 0.5 MAC in the immediate post-bypass period.

Our study surprisingly did not find a statistically significant increase in new atrial fibrillation or acute kidney injury in patients exposed to inotropes and vasoconstrictors, as other studies have reported. However, there were statistically significant differences in longer ICU stay, total length of stay, and slightly longer time to extubation in those exposed to inotropes and vasoconstrictors. While these differences are not exceptional, they are powerful when considering the number of cardiac surgery patients per year and the cost of these extra inpatient days. In our institution these infusions were maintained for an average of 50 h postoperatively in the ICU, which most likely is longer than clinically necessary.

4.3. Limitations and Speculation

Our study has several important limitations. First, it has inherent bias associated with a retrospective chart review. We obtained many demographic variables to try and adjust for the differences between patients as well as using a propensity score to adjust for differences. There is always the possibility that we did not collect particular data that may have been meaningful in creating the propensity score. Inherent in medicine, there can be considerable provider-to-provider differences in style of administering anesthesia. We had many different anesthesiologists and surgeons providing cardiac surgical care, which adds to the different approaches used to manage patients in the post-bypass period, as

well as for the treatment of low cardiac output syndrome. Therefore, it is impossible to know exactly the minute-to-minute clinical decision making from a rapidly fluctuating hemodynamic status that is common during cardiac surgery. We also did not collect data on specific hemodynamic measurements before and after CBP. We did not collect data on intraoperative awareness, or other drug infusions during the post bypass period such as opioids or benzodiazepines. Furthermore, it was not possible to collect data on intraoperative volume status, as this was not reliably recorded in the medical chart. Our institution routinely uses isoflurane during cardiac surgery, thus our data on other inhalational agents are limited. Furthermore, we did not further stratify MAC levels (i.e., 30 min of exposure over 0.75 MAC, over 1 MAC) nor record the maximum level of MAC and time of exposure, which may have provided even more information regarding the relationship with the use of inotropes and vasoconstrictors.

5. Conclusions

An $ET_{ISO} \geq 0.5_{MAC}$, $30_{\ min}$ during the weaning and post-CPB period in elective cardiac surgery was a significant independent predictor of the use of inotropic and/or vasoconstrictor infusion use during the post-bypass period. Avoiding higher doses of isoflurane and utilizing intravenous anesthetic agents for hypnosis and analgesia during the vulnerable parts of a cardiac procedure can possibly harness the beneficial effects of inhaled anesthetics while avoiding starting inotropes and vasoconstrictors. Further studies focusing on a prospective cohort or randomized trial could work to define the most clinically appropriate dose of isoflurane in order to avoid or reduce inotrope and vasoconstrictor use while utilizing depth of anesthesia guidance, such as BIS monitoring.

Author Contributions: T.A.L. and C.E.G.-L. collected & analyzed data, and wrote and revised manuscript. P.K.H., T.E.G. and M.A.M. collected data. G.D. processed the statistics and assisted with editing the Methods Section. R.K.M. assisted on project design, and manuscript revision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Henry Ford Hospital (IRB No. 11011).

Informed Consent Statement: Patient consent was waived due to retrospective nature of the study.

Data Availability Statement: Data presented in this article was collected by the research team and is not found elsewhere. It is contained within the tables presented within the article.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

$ET_{ISO} \geq 0.5_{MAC}$, $30_{\ min}$: age-adjusted end-tidal minimum alveolar concentration of greater than 0.5 for more than 30 cumulative minutes during weaning from cardiopulmonary bypass and the post-bypass period; MAC: minimum alveolar concentration; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; ASA: American society of Anesthesiology; ICU: intensive care unit; SD: standard deviation.

References

1. Nielsen, D.V.; Hansen, M.K.; Johnsen, S.P.; Hansen, M.; Hinsholm, K.; Jakobsen, C.-J. Health outcomes with and without use of inotropic therapy in cardiac surgery: Results of a propensity score-matched analysis. *Anesthesiology* **2014**, *120*, 1098–1108. [CrossRef]
2. Fellahi, J.-L.; Parienti, J.-J.; Hanouz, J.-L.; Plaud, B.; Riou, B.; Ouattara, A. Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome: Propensity-adjusted analyses. *Anesthesiology* **2008**, *108*, 979–987. [CrossRef]

3. Fleming, G.A.; Murray, K.T.; Yu, C.; Byrne, J.G.; Greelish, J.P.; Petracek, M.R.; Hoff, S.J.; Ball, S.K.; Brown, N.J.; Pretorius, M. Milrinone use is associated with postoperative atrial fibrillation after cardiac surgery. *Circulation* **2008**, *118*, 1619–1625. [CrossRef] [PubMed]
4. Shahin, J.; De Varennes, B.; Tse, C.W.; Amarica, D.-A.; Dial, S. The relationship between inotrope exposure, six-hour postoperative physiological variables, hospital mortality and renal dysfunction in patients undergoing cardiac surgery. *Crit. Care.* **2011**, *15*, R162. [CrossRef] [PubMed]
5. Frassdorf, J.; De Hert, S.; Schlack, W. Anaesthesia and myocardial ischaemia/reperfusion injury. *Br. J. Anaesth.* **2009**, *103*, 89–98. [CrossRef] [PubMed]
6. El Dib, R.; Guimaraes Pereira, J.E.; Agarwal, A.; Gomaa, H.; Ayala, A.P.; Botan, A.G.; Braz, L.G.; De Oliveira, L.D. Inhalation versus intravenous anaesthesia for adults undergoing on-pump or off-pump coronary artery bypass grafting: A systematic review and meta-analysis of randomized controlled trials. *J. Clin. Anesth.* **2017**, *40*, 127–138. [CrossRef] [PubMed]
7. Stevens, W.C.; Cromwell, T.H.; Halsey, M.J.; Eger, E.I., II; Shakespeare, T.F.; Bahlman, S.H. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. *Anesthesiology* **1971**, *35*, 8–16. [CrossRef] [PubMed]
8. Pagel, P.S.; Kampine, J.P.; Schmeling, W.T.; Warltier, D.C. Influence of volatile anesthetics on myocardial contractility in vivo: Desflurane versus isoflurane. *Anesthesiology* **1991**, *74*, 900–907. [CrossRef] [PubMed]
9. Hettrick, D.A.; Pagel, P.S.; Warltier, D.C. Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency. *Anesthesiology* **1996**, *85*, 403–413. [CrossRef] [PubMed]
10. Merin, R.G. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? *Anesthesiology* **1981**, *55*, 398–408. [CrossRef] [PubMed]
11. Malan, P.T., Jr.; DiNardo, J.A.; Isner, J.R.; Frink, E.J., Jr.; Goldberg, M.; Fenster, P.E.; Brown, E.A.; Depa, R.; Hammond, L.C.; Mata, H. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. *Anesthesiology* **1995**, *83*, 918–928. [CrossRef] [PubMed]
12. Lorsomradee, S.; Cromheecke, S.; Lorsomradee, S.; De Hert, S.G. Cardioprotection with volatile anesthetics in cardiac surgery. *Asian Cardiovasc. Thorac. Ann.* **2008**, *16*, 256–264. [CrossRef] [PubMed]
13. Julier, K.; da Silva, R.; Garcia, C.; Bestmann, L.; Frascarolo, P.; Zollinger, A.; Chassot, P.-G.; Schmid, E.R.; Turina, M.I.; von Segesser, L.K.; et al. Preconditioning by sevoflurane Decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinDed, placebo-controlled, multicenter study. *Anesthesiology* **2003**, *98*, 1315–1327. [CrossRef] [PubMed]
14. Tomai, F.; De Paulis, R.; de Peppo, A.P.; Colagrande, L.; Caprara, E.; Polisca, P.; De Matteis, G.; Ghini, A.S.; Forlani, S.; Colella, D.; et al. Beneficial impact of isoflurane during coronary bypass surgery on troponin I release. *G. Ital. Di Cardiol.* **1999**, *29*, 1007–1014.
15. Haroun-Bizri, S.; Khoury, S.S.; Chehab, I.R.; Kassas, C.M.; Baraka, A. Does isoflurane optimize myocardial protection during cardiopulmonary bypass? *J. Cardiothorac. Vasc. Anesth.* **2001**, *15*, 418–421. [CrossRef] [PubMed]
16. Warltier, D.C.; al-Wathiqui, M.H.; Kampine, J.P.; Schmeling, W.T. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* **1988**, *69*, 552–565. [CrossRef] [PubMed]
17. De Hert, S.G.; Cromheecke, S.; ten Broecke, P.W.; Mertens, E.; De Blier, I.G.; Stockman, B.A.; Rodrigus, I.E.; van der Liden, P.J. Effects of propofol, Desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. *Anesthesiology* **2003**, *99*, 314–323. [CrossRef] [PubMed]
18. Landoni, G.; Lomivorotov, V.V.; Neto, C.N.; Monaco, F.; Pasyuga, V.V.; Bradic, N.; Lembo, R.; Gazivoda, G.; Likhvantsev, V.V.; Lei, C.; et al. Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery. *N. Engl. J. Med.* **2019**, *380*, 1214–1225. [CrossRef] [PubMed]