RISK OF INTRAOPERATIVE HYPOTENSION IN CYSTIC FIBROSIS PATIENTS WITH AND WITHOUT DIABETES: A PILOT STUDY

A THESIS
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

IOANNA APOSTOLIDOU

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

ANTOINETTE MORAN

DECEMBER 2012

Acknowledgements

I would like to give acknowledgement to the following individuals:

1. Antoinette Moran, MD, for being my mentor in this project and introducing to me the cystic fibrosis population.
2. Elif Cingi, MD, for being an important collaborator and for her contribution in the in the conduction of this project.
3. Scott Lunos, statistician at the Biostatistical Design and Analysis Center (BDAC), University of Minnesota, for performing the statistical analysis.
4. Emily Williams and Melissa Haehn, medical students, for identifying eligible participants from the Cystic Fibrosis Database, and collecting and entering the data in our dataset.

Abstract

Objective

In this pilot study, we evaluated the incidence and severity of intraoperative hypotension and its relationship to CAN in patients with CFRD. We compared the CFRD patients to cystic fibrosis patients without diabetes (CF-noDM) and with type 1 DM patients.

Methods

A retrospective chart review of perioperative records was performed on an existing cohort of CFRD patients in whom diabetic neuropathy status had been previously characterized (n=25). Testing for CAN included the variation in heart rate response to deep breathing (HRDB) and to a Valsava maneuver (Valsava ratio,VR). The primary endpoints were the occurrence and severity of intraoperative hypotension. Intraoperative data on CFRD patients were compared to data collected from CF-noDM (n=56) and T1DM (n=6).

Results

More than half of CF patient-surgeries experienced hypotension during anesthesia and the odds of hypotension did not significantly differ between groups (CFRD-52%, CF-noDM-56%, T1DM-38%). However, the severity of hypotension was worse in those with diabetes. During hypotension, the mean decrease in SBP was 32% for CFRD and mmHg 33% for T1DM, compared to 24% for CF-noDM (p=0.03, CFRD vs CF-noDM). In CFRD patients, an abnormal VR was associated with a greater risk of hypotension (88% vs. 44%, p=0.0046) and greater need for intraoperative vasopressors (p= 0.04) as compared to normal VR.

Conclusion

CF patients are prone to develop intraoperative hypotension which is more severe in those with diabetes and it is associated with an abnormal VR. Larger prospective studies are needed to confirm our findings.

Table of Contents

List of Tables

List of Figures

INTRODUCTION

Hypotension during general anesthesia may compromise vital organ perfusion, leading to significant morbidity and mortality (1-7). This is of particular concern in patients with type 1 (T1DM) and type 2 (T2DM) diabetes, who are at 2 to 3 times higher risk of perioperative morbidity and mortality compared to individuals without diabetes (8,9). Previous small-scale studies demostrated that diabetic patients have blunted hemodynamic response to intubation and extubation resulting to a greater decline in heart rate and blood pressure during general anesthesia (10). This has been explained partially by damage of autonomic nerve fibers and interruption of corresponding cardiovascular reflexes due to pre-existing cardiovascular autonomic neuropathy (CAN) (10,11). CAN is a common form of autonomic dysfunction found in patients with diabetes mellitus patients. Clinical manifestations of CAN include orthostatic hypotension, exercise intolerance, asymptomatic ischemia, intraoperative cardiovascular lability, and increased risk of mortality. Reduction of heart rate variability and high resting heart rate are early sings of CAN, and may be apparent within one year of T1DM and two years of T2DM. Previous studies in patients undergoing surgery demostrated that diabetic patients with CAN have a higher need of vasopressor support intraoperatively, are at higher risk of intraoperative hypothermia and have a depressed ventilatory drive in response to hypoxia (12-14).

The etiology of CAN in diabetics is multifactorial and includes metabolic, neurovascular, autoimmune and neurohormonal insults to the nerve fibers. Cystic fibrosis related diabetes (CFRD), is a unique type of secondary diabetes that occurs in 15-20% of adolescents and 40-50% of adults cystic fibrosis (CF) (15). CFRD differs pathophysiologically and clinically from T1DM and T2DM, and is considered a distinct clinical entity (15). It is characterized by severe but not complete insulin deficiency and only modest insulin resistance. Lipid levels and blood pressure (BP) are generally normal, and, unlike patients with other forms of diabetes, CFRD patients are not at high risk for atherosclerotic cardiovascular disease. They do, however, share the increased risk of microvascular complications characteristic of those with T1DM and T2DM (15). Approximately 50% of patients who had CFRD for 10 years or more had diabetic neuropathy; about half of those experienced CAN (16).

Patients with CFRD frequently undergo surgical procedures requiring general anesthesia (17). The intraoperative hemodynamic behavior of CFRD patients has not been previously investigated and it is unknown whether CFRD patients have increased risk for hemodynamic lability similar to that of patients with T1DM and T2DM. This has important implications for physicians involved in the anesthetic planning and perioperative management of the CFRD patients. The goal of this pilot study was to evaluate the incidence and severity of intraoperative hypotension in patients with CFRD and its relation to CAN. We compared these data to intraoperative risk in CF patients without diabetes (CF-noDM) and a small cohort of patients with T1DM.

METHODS

Study Design and Population

A retrospective chart review was performed on an existing cohort of CFRD patients in whom diabetic neuropathy status had been previously characterized (16). These data were compared to intraoperative risk data collected from CF patients without diabetes (CF-noDM) and a small cohort of patients with T1DM (18). The analysis was limited to the most common surgeries in CF including abdominal, thoracic and ear-nose-throat surgical procedures. Orthopedic, neurological, and vascular surgeries, as well as endoscopic procedures were excluded because of potential confounding factors such as very short or very long anesthesia duration and different anesthesia techniques. All patients received general endotracheal anesthesia, including a volatile agent, opioids, muscle relaxants, and benzodiazepines as per standard practice at the University of Minnesota (UM).

Fifty-nine adult patients with CFRD with fasting hyperglycemia underwent extensive neurologic testing in 2006 (16). Twenty-five of these had at least one applicable surgical procedure within 2 years of this testing (2004-2008), and they form the CFRD cohort for the current report. Each CFRD patient was matched to at least 1 and up to 4 CF-noDM patients (depending on the number of appropriate subjects available) who underwent surgery at UM, 2000-2009. Non-diabetic status was established by routine annual oral glucose tolerance testing. We matched patient based on age ±2 and surgery category (abdominal, thoracic or ear-nose-throat). Two independent investigators verified the accuracy of matching criteria. The T1DM comparison group was drawn from a small cohort of T1DM patient that had been entered in another study. The study included thirteen T1DM candidates for pancreas transplantation with a prior diagnosis of gastroparesis (18). From those, only six subjects underwent surgeries at the UM between 2004-2008 and comprised our T1DM comparison group.

Neurological evaluations

Neurological and autonomic nervous system evaluations were performed by a neurologist experienced in neuropathy assessment, and have been described in detail in another study (17). The evaluations included assessment of sensation (touch, pinprick and vibration), strength, and reflexes, nerve conduction studies and tests of cardiovagal function. Cardiovagal tests included heart rate response to deep breathing (HRDB) and Valsava maneuver (Valsava ratio,VR), and were considered indicative of CAN. The heart rate (HR) change during deep breathing is maximal at a rate of six breaths per minute and is calculated based on the largest R-R interval. A HRDB value <18 is considered abnormal for subjects up to the age of 40 years and a HRDB value < 16 for subjects between the ages of 41 to 50. (19). To measure the HR response to Valsava maneuver, the patient is asked to blow into a tube to maintain a column of mercury at 40 mm Hg for 15 seconds. The VR is calculated by dividing the maximum HR generated by the Valsava maneuver by the minimum heart rate occurring within 30 sec of the peak HR. A VR value < 1.5 is considered abnormal for subjects up to the age of 40 years and a VR value < 1.45 for subjects between the ages of 41 and 50 (19). All CFRD subjects with autonomic testing were ≤ 50 years of age.

Intraoperative hemodynamic assessment

The primary endpoints, collected from the intraoperative anesthesia records, were 1) the occurrence of intraoperative hypotension, defined as systolic blood pressure (SBP) <90 mmHg, and 2) the severity of hypotension, defined as maximum downward divergence from the baseline value and expressed as both the absolute decrease from baseline and the percentage change from baseline. Baseline value was the first BP measurement taken in the preoperative area prior to any medication administration. Baseline BP was measured with an oscillometric noninvasive device. Intraoperative BP was measured either by the oscillometric method or with an arterial cannula, recorded at 5-min intervals.

Bradycardia (HR <50 beats per min) and the use of intraoperative vasopressor medications (ephedrine, phenylephrine, atropine, glycopyrrolate) were recorded. Additional data collected included age, gender, weight, height, type and date of surgery, if surgery was emergent, American Society of Anesthesiologists (ASA) physical status classification (1=normal healthy patient, 2=mild systemic disease, 3=severe systemic disease, 4= severe systemic disease that is a constant threat to life, 5=moribund patient not expected to survive without the operation), medical comorbidities, and medications. Data were extracted from the medical record by an investigator blinded to the results of the neurological evaluations, and confirmed by a second blinded investigator for reliability.

Statistical Analyses

Descriptive statistics were calculated for baseline demographics, operative data outcomes and neurological evaluations for each group. Analysis of variance and t-tests for continuous measures and Fisher's exact tests for categorical measures were used to compare baseline data between groups. To control for type I error and unequal group sizes, we did pairwise comparison using the Tuckey-Kramer method to find which groups means are different. We also compared VR and HRDB measures between the CFRD and T1DM groups. Generalized estimating equations (GEE) models were used to analyze the operative data outcomes between groups. GEE was used to account for the correlated outcome data (within patient correlation, multiple surgeries per patient). GEE models were also used to assess the relationship between intraoperative hypotension and autonomic neuropathy in CFRD patients and the risk for hypotension in future surgeries of CF patients. Because of the small sample size adjustments were made for two covariates, anesthesia time and baseline SBP. P-values less than 0.05 were deemed statistically significant. P-values were not adjusted for the multiple comparisons unless otherwise indicated. SAS V9.1.3 was used for the analyses.

RESULTS

Subjects

Table 1 shows the baseline (time of the first surgery) characteristics and Table 2 presents the operative data of study subjects. The CF groups did not differ from each other in gender or body composition. The T1DM group tended to be somewhat older and heavier (although weight was not significantly different). In pairwise comparison, CFRD had significantly higher baseline SBP (129±19 vs.118±15 mmHg, p=0.004) and HR (92±17 vs. 83±16 beats per minute, p=0.02) compared to CF-noDM, and these parameters more closely resembled patients with T1DM. Pre-existing hypertension was uncommon in CF but was universally present in the T1DM cohort. All T1DM patients and 35% of CFRD patients had evidence of autonomic neuropathy by at least one measure. Abnormal VR and HRDB were found in 80% and 100% of T1DM patients and in 26% and 30% of CFRD patients, respectively. Two CFRD and one T1DM subjects did not have autonomic testing. Autonomic testing was not performed in CF-noDM.

Table 1. Characteristics of Study Groups.

	CFRD	CF-noDM	T1DM	P-Value CFRD vs CF-noDM	P-Value CF Total vs T1DM
BASELINE DATA					
N, subjects	25	56	6	NA	NA
N,female (%)	14 (56%)	25 (45%)	4 (67%)	0.47	0.43
Age, years	34±9	29±10	44±9	0.02*	0.002*
Weight, kg	62±12	66±18	75±19	0.36	0.13
Height, cm	167±8	166±11	166±9	0.82	0.97
BMI kg/m2	22 ±4	24±7	25 ±2	0.36	0.66
HR beats per min	92±17	83±16	93±19	0.02*	0.31
SBP mmHg	129±19	118±15	124±16	0.004*	0.75
DBP mmHg	79±14	72±12	77±17	0.02*	0.68
N, subjects with history of HTN (%)	4 (16%)	2 (4%)	6 (100%)	0.07*	<0.0001*
N, subjects with abnormal VR (%)	6 (26%)	NA	4 (80%)	NA	0.04*
N, subjects with abnormal HRDB (%)	7 (30%)	NA	5 (100%)	NA	0.01*

*indicates P-value < 0.05. Data are expressed as mean ±SD unless otherwise indicated. ANOVA for continuous variables, Fisher's exact test for categorical variables, pairwise comparisons using Tukey-Kramer adjustment.

Cystic fibrosis related diabetes (CFRD), Cystic fibrosis patients without diabetes (CF-noDM), Type 1 diabetes (T1DM), Hypertension (HTN). Baseline refers to the time of the first surgery.

Abnormal Valsalva ratio (VR) and abnormal HR variation during deep breathing (HRDB) were defined in the methods.

Table 2. Operative Data of Study Groups

	CFRD	**CF-noDM**	**T1DM**	**P-Value CFRD vs CF-noDM**	**P-Value CF Total vs T1DM**
OPERATIVE DATA					
N, surgeries (average per person)	42 (1.7)	77 (1.4)	21 (3.5)		NA
ASA PS classification 1 2 3 4	 0% 8% 88% 4%	 2% 13% 86% 0%	 0% 0% 100% 0%	0.57	1.00
Anesthesia Time, min	228±266	164±124	340±147	0.14	0.04*
N, surgeries with hypotension (%)	22 (52%)	43 (56%)	8 (38%)	0.78	0.66
SBP decrease during hypotension, mmHg	42±18	28±15	43±19	0.03*	0.20
%SBP decrease during hypotension	32±10	24±10	33±11	0.03*	0.18
N, surgeries with bradycardia (%)	1 (2%)	6 (8%)	0 (0%)	0.19	NA

*indicates P-value < 0.05. ANOVA for continuous variables, Fisher's exact test for categorical variables, pairwise comparisons with Tukey-Kramer adjustment. Generalized estimating equations model was used for the analysis of hypotension. Data are expressed as mean ±SD unless otherwise indicated.

Cystic fibrosis related diabetes (CFRD), Cystic fibrosis patients without diabetes (CF-noDM), Type 1 diabetes (T1DM).

Operative data are from all surgeries. American Society of Anesthesiologists (ASA) Physical Status Classification. Hypotension was defined as SBP < 90 mmHg.

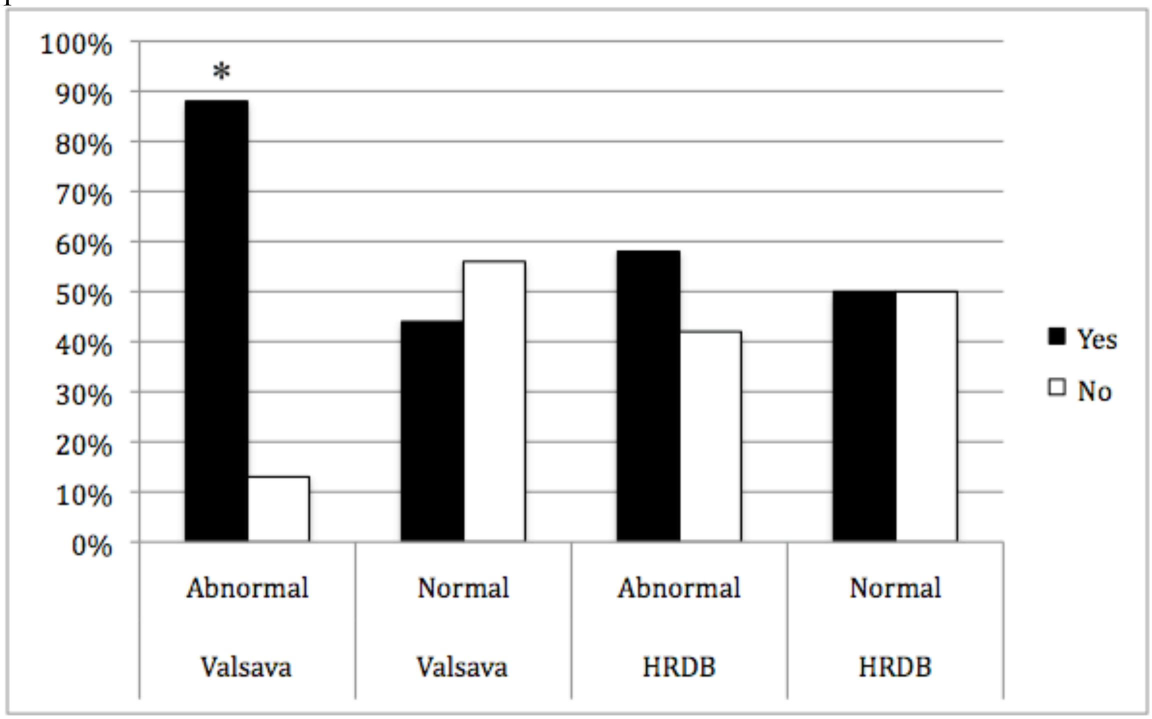
Prevalence of intraoperative hypotension and bradycardia

Twenty-five CFRD patients had 42 surgeries, 56 CF-noDM patients had 77 surgeries, and 6 T1DM patients had 21 surgeries (Table 2). Illness severity by ASA criteria was similar across the groups. Anesthesia time tended to be greater in T1DM when compared to CF patients (p=0.04). More than half of CF patient-surgeries experienced hypotension during anesthesia. After adjusting for anesthesia time, the odds of hypotension did not significantly differ between groups (CFRD-52%, CF-noDM-56%, T1DM-38%) (p=0.90). However, the severity of hypotension was worse in those with diabetes as measured by both the absolute value of SBP decrease and % SBP decrease from baseline. During hypotension, the mean decrease in SBP was 42±18 mmHg (32%) for CFRD and 43±19 mmHg (33%) for T1DM, compared to 28±15 (24%) for CF-noDM (p=0.03, CFRD vs CF-noDM). After adjusting for anesthesia time, the difference between CFRD and CF-noDM remained significant only in the absolute value of SBP decrease (p=0.03) and not in the % SBP decrease from baseline (p=0.07).

Relationship of intraoperative hypotension to autonomic neuropathy in CFRD patients

Data from the CFRD patients only were analyzed to determine the impact of autonomic dysfunction on intraoperative hypotension using a GEE model and after adjusting for anesthesia time and baseline SBP. CFRD patients with abnormal VR became hypotensive in 88% of their surgeries; in contrast, CFRD patients with normal VR were hypotensive in 44% of surgeries (OR:15.1, 95%CI:2.3, 98.3 p=0.0046) (Figure 1). CFRD patients with abnormal VR were more likely (OR=7.8, 95% CI: 1.1, 57.5) to have been given intraoperative vasopressors compared to CFRD patients with normal VR (p= 0.04).

Figure 1. Relationship of intraoperative hypotension to autonomic neuropathy in CFRD patients.



* denotes statistically significant difference between abnormal and normal VR.
The percentage of CFRD patients with normal and abnormal autonomic nerve function tests who did (black bars) or did not (white bars) experience hypotension during surgery.
Valsalva ratio (VR), Heart rate deep breathing (HRDB)

Abnormalities in HRDB did not have the same predictive value for assessing risk of operative hypotension, since approximately half of patients with or without abnormal HRDB experienced this complication. However, CFRD patients with abnormal HRDB were more likely (OR: 8.9, 95% CI: 1.3, 58.6) to have been given intraoperative vasopressors (p=0.02). This may have been prompted by heart rate changes during surgery rather than BP instability since CFRD patients with either abnormal VR or HRDB had lower intraoperative HR values (VR mean difference -7.1, 95% CI: -12.9, -

1.4; HRDB mean difference -8.1, 95% CI: -13.4, -2.8).

Risk of Future Surgeries

A GEE model was used to analyze the association between the occurrence of hypotension in the first surgery and the risk for hypotension in subsequent surgeries in CF patients (Table 3). There were 23 patients who had multiple surgeries (11 CFRD, 12 CF-noDM,) for a total of 61 surgeries. More than half (57%) had hypotension during the first surgery. Patients were more likely (OR: 2.7, 95% CI: 0.8, 8.6) to have hypotension in future surgeries if they had hypotension in the first surgery, however this was not statistically significant (p=0.20).

Table 3. Risk of Future Surgeries.

	Hypotension in 1st Surgery n=20	No Hypotension in 1st Surgery n=18
Future hypotension-Yes	13 (65%)	8 (44%)
Future hypotension-No	7 (35%)	10 (56%)

Occurrence of hypotension in a future surgery relative to the occurrence of hypotension in a first surgery, in 23 CF patients who had more than 1 surgery (38 successive surgeries).

DISCUSSION

Diabetes is a known risk factor for intraoperative hypotension, and we hypothesized that this would also be true in CFRD. Unexpectedly, this life-threatening surgical complication occurred in more than 50% of CF patients irrespective of diabetes status. The high prevalence of hypotension is somewhat surprising given the relatively young age of the CF patients (median=29), although it is similar to that published for older individuals (1). While diabetes did not increase the frequency of operative hypotension in CF patients, the magnitude of the drop in SBP was more severe in those with CFRD. Within CFRD, the presence of an abnormal Valsalva ratio was a very strong predictor of intraoperative hypotension (88%). Both VR and HRDB predicted the need for intraoperative vasopressor support. For CF patients, hypotension during one surgery was associated with nearly a three-fold increase of hypotension odds in subsequent surgeries, although not statistically significant.

Hypotension occurs frequently during general anesthesia. There is great variability in the reported incidence of intraoperative hypotension because of the lack of a reliable and consistently applied definition. For instance, the incidence of intraoperative hypotension varies between 5% to 99% based on the chosen definition (1). Most hypotension definitions rely on either an absolute or relative decrease of SBP or MAP from a baseline value with or without a specific duration. We used an absolute SBP < 90 mmHg as our definition because this threshold commonly triggers treatment with vasopressors or fluids. The population we selected for this study represents a young adult population with a chronic illness and multiple comorbidities. Is not surprising that we found a high percentage of surgeries with hypotension in all three groups (52% in CFnonDM, 56% in CFRD and 38% in T1DM).

If BP falls below a certain threshold to maintain organ perfusion during surgery, there is significant risk of ischemia, renal compromise, cardiac and neurological complications, and death (2-7). The etiology of intraoperative hypotension is multifactorial and is primarily due to systemic vasodilation, negative inotropic action, inhibition of sympathetic outflow, depression of baroreflex function induced by most of the anesthetics, or major fluid shifts and blood loss (20-27). Intravenous induction agents such as propofol and thiopental, as well as benzodiazepines, may depress basal levels of sympathetic activity (20,21,27). An induction dose of thiopental or twice the induction dose of propofol decreased renal sympathetic nerve activity and mean arterial pressure to the same degree (about 20%) in animals and attenuated baroreceptor sensitivity (21). Conversely, an induction dose of etomidate increased renal sympathetic nerve activity without causing a reduction in MAP (28). Inhalation anesthetics may all induce a dose dependent hypotension due to a direct effect on vascular smooth muscle and vasodilation. Increasing concentrations of inhalation anesthetics may also depress sympathetic activity and baroreflex sensitivity, but they return to a normal level when a steady state of inhalation anesthetic is reached (22,29,30). An intact sympathetic nervous system along with the renin-angiotensin and arginin-vasopressin system play a major role in maintaining BP under anesthesia (30-34). When disruption of the sympathetic nervous system, such as CAN occurs, maintenance of BP relies solely on the renin-angiotensin and arginin-vasopressin. In these situations the body's compensatory mechanisms to hypotension induced by general anesthesia may be greatly impaired. Previous studies in diabetic and nondiabetic patients undergoing general anesthesia demonstrated that hypotensive risk was greater in the presence of CAN (10,11,14). Similarly, we found higher risk of hypotension in CFRD patients with an abnormal VR.

The diagnosis of CAN is based on a battery of autonomic tests that include: cardiovagal HR tests, laboratory indices of adrenergic function, and sudomotor tests (35). The cardiovagal HR tests include HRDB, VR and HR response to standing. They are well-established tests of autonomic function and simple to perform. The autonomic evaluation of our CFRD cohort included only the first two of the three proposed tests for evaluation of the cardiovagal function. According to a three-stage model proposed for the diagnosis of diabetic autonomic neuropathy, an abnormal HRDB alone is indicative of an early stage, while an abnormal VR is indicative of intermediate stage of the condition (36). Based on the above criteria, almost 1/3 of our CFRD patients were in an early stage of autonomic neuropathy and 1/4 of them were in an intermediate stage. In our study, only the CFRD patients in more advanced autonomic neuropathy (abnormal VR) were prone to hypotension and not those in early stages (abnormal HRDB). Likewise, diabetic patients with greater autonomic impairment required BP support intraoperatively in a previous study (10). Diabetes is a known risk factor for the development of life-threatening hypotension under anesthesia, and autonomic neuropathy has been implicated as a significant contributing factor (8-10, 14).

Other studies evaluating the relationship of heart rate variability (HRV) abnormalities (another test of cardiac autonomic function) with intraoperative hemodynamic events showed conflicting results. In a study of diabetic patients undergoing coronary artery bypass surgery, Keyl et al. did not find any correlations between preoperative cardiovascular autonomic function tests and BP change on induction of anesthesia (37). These authors attributed the different results to differences in the population (with coronary artery disease) and anesthetic technique (etomidate vs. propofol for induction), as well as to interference of beta-blockers and calcium antagonists on autonomic testing results. Indeed, in patients who are taking beta-blockers, both VR and HRDB are significantly lower than in those who are not (38).

In the current report, the severity of hypotension was greater in CF patients with diabetes than in those without diabetes, confirming the importance of diabetes as a risk factor for perioperative morbidity in the CF population. However, the prevalence of hypotension was similar in CF patients with and without diabetes, suggesting that factors intrinsic to CF may also be important. Cystic fibrosis is a chronic genetic disease with severe metabolic abnormalities, nutritional deficiencies, and immunologic compromise. Autonomic neuropathy has been reported in association with severe chronic disease such as chronic liver disease, renal failure, amyloid, nutritional disorders, and malignancy. Preliminary studies have indicated that autonomic neuropathy may exist in CF regardless of the presence of DM (39-41). Due to the lack of autonomic testing in CF-noDM, we were not able to explore the presence of autonomic neuropathy in CF-noDM.

When BP falls below the lower threshold of the autoregulatory plateau, there is a significantly increased risk for hypoperfusion and ischemia. Refractory intraoperative hypotension may lead to significant morbidity and mortality (2-7). Charlson et al.

demonstrated that both hypotension and hypertension were associated with cardiac and renal complications in elective noncardiac surgery (4). Similarly, a low mean arterial pressure (50-60 mmHg) during CPB was associated with higher mortality, stroke, and cardiac complications compared to high mean arterial pressure (80-100 mmHg) in a prospective randomized study (7). Neurological outcome is worse in patients who develop hypotension during endovascular intervention under general anesthesia for acute stroke. All the above observations are based on cohort studies, and no direct evidence supported by a randomized study of a causal relationship between hypotension and poor patient outcome exists. Randomized studies are recommended when there is a state of equipoise and no consensus in clinical practice. It is the standard of practice to prevent and treat hypotension during anesthesia; therefore, it would be unethical to conduct a study and expose patients to a valid risk. It is important for anesthesiologists and physicians involved in the perioperative care of patients to understand the risk of intraoperative hypotension in vulnerable populations in order to develop pre-operative screening and management strategies to improve patient outcomes.

Limitations

Our study has a number of important limitations, the most important of which are its retrospective design and the limited number of T1DM controls. We used previously collected data that might be inaccurate, incomplete or biased. Handwritten anesthesia records report BP and HR values every 5 minutes and may not be capturing all the values accurately. The small size of T1DM patients limited our ability to evaluate the effect of age as a covariate in the GEE models. Another reason to support our decision to exclude age is that our cohort's age group is lower than the age cutoff value (> 50 years) that has been shown to be a risk factor for hypotension in previous studies. We limited our covariates to the clinically most relevant, such as anesthesia time and baseline SBP. However, we cannot be sure that age or other unknown covariates might have influenced our results. An additional limitation is the lack of autonomic testing data in the CF-noDM patients. One further concern with our study is that finding no significant association might be due to small sample size and limited statistical power. Nonetheless, we were able to provide new insights on how CF patients respond to anesthesia and surgery. Our data are preliminary and should be confirmed in future prospective studies.

CONCLUSION

CF patients are subject to numerous diagnostic or therapeutic surgeries related to their underlying disease (17). The current report has shown that whether or not they have diabetes, CF patients are prone to develop intraoperative hypotension. Hypotension is more severe, however, in those with diabetes. In CFRD, the presence of CAN is associated with hypotension risk. The VR and the HRDB are simple autonomic nerve function tests that can be performed easily and quickly at the bedside as part of an anesthesia risk assessment. Larger, prospective studies are needed to confirm the findings of this pilot study and to explore associations of CAN and surgical hypotension in CF patients without diabetes.

REFERENCES

1. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. "Incidence of Intraoperative Hypotension as a Function of the Chosen Definition: Literature Definitions Applied to a Retrospective Cohort Using Automated Data Collection." Anesthesiology 2007;107:213-20.
2. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. "Preoperative Characteristics Predicting Intraoperative Hypotension and Hypertension Among Hypertensives and Diabetics Undergoing Noncardiac Surgery." Ann Surg 1990;212:66-81.
3. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. "Intraoperative Blood Pressure: What Patterns Identify Patients at Risk for Postoperative Complications?" Ann Surg 1990;212:567-80.
4. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Fairclough GP Jr, Shires GT. "The Preoperative and Intraoperative Hemodynamic Predictors of Postoperative Myocardial Infarction or Ischemia in Patients Undergoing Noncardiac Surgery." Ann Surg 1989;210:637-48.
5. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M. "Intraoperative Tachycardia and Hypertension Are Independently Associated with Adverse Outcome in Noncardiac Surgery of Long Duration." Anesth Analg 2002;95:273-7.
6. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. "Intraoperative Hemodynamic Predictors of Mortality, Stroke, and Myocardial Infarction After Coronary Artery Bypass Surgery." Anesth Analg 1999;89:814-22.
7. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D, et al. "Improvement of Outcomes After Coronary Artery Bypass: A randomized trial comparing intraoperative high versus low mean arterial pressure." J Thorac and Cardiovasc Surg 1995;110:1302-11; discussion 1311-4.
8. Vinik AI, Ziegler D. "Diabetic Cardiovascular Autonomic Neuropathy." Circulation 2007;115;387-97.
9. Ziegler D. "Diabetic Cardiovascular Autonomic Neuropathy: Prognosis, Diagnosis and Treatment." Diabetes Met Rev 1994;10:339-83.
10. Burgos LG, Ebert TJ, Asiddao C, Turner LA, Pattison CZ, Wang-Cheng R, Kampine JP. "Increased Intraoperative Cardiovascular Morbidity in Diabetics with Autonomic Neuropathy." Anesthesiology 1989;70:591-7.
11. Latson TW, Ashmore TH, Reinhart DJ, Klein KW, Giesecke AH. "Autonomic Reflex Dysfunction in Patients Presenting for Elective Surgery Is Associated with Hypotension after Anesthesia Induction." Anesthesiology 1994;80:326-37.
12. Kitamura A, Hoshino T, Kon T, Ogawa R. Patients with diabetic neuropathy are at risk of a greater intraoperative reduction in core temperature. *Anesthesiology*. 2000;92:1311–1318.
13. Sobotka PA, Liss HP, Vinik AI. Impaired hypoxic ventilatory drive in diabetic patients with autonomic neuropathy. *J Clin Endocrinol Metab*. 1986;62:658–663.
14. Knuttgen D, Buttner Belz U, Gernot A. Unstable blood pressure during anesthesia

in diabetic patients with autonomic neuropathy. *Anasth Intensivther Notfallmed*. 1990;25:256 –262.

15. Moran A, Becker D, Casella SJ, Gottlieb PA, Kirkman MS, Marshall BC, Slovis B, CFRD Consensus Conference Committee. “Epidemiology, Pathophysiology, and Prognostic Implications of Cystic Fibrosis-Related Diabetes.” Diabetes Care 2010;33:2677-83.
16. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, Moran A. “Microvascular Complications in Cystic Fibrosis-Related Diabetes.” Diabetes Care 2007;30:1056-61.
17. Olsen MM, Gauderer MW, Girz MK, Izant RJ Jr. “Surgery in Patients With Cystic Fibrosis.” J Ped Surg 1987;22:613-8.
18. Selim MM, Wendelschafer-Crabb G, Redmon JB, Khoruts A, Hodges JS, Koch K, Walk D, Kennedy WR. Gastric mucosal nerve density: a biomarker for diabetic autonomic neuropathy? Neurology. 2010 Sep 14;75(11):973-81.
19. Low PA. “Laboratory evaluation of autonomic function.” Clinical Autonomic Disorders: Evaluation and Management. Ed. PA Low. Philadelphia: Lippincott-Raven, 1997. 2nd ed. 179-208.
20. Ebert TJ, Kanitz DD, Kampine JP. “Inhibition of Sympathetic Neural Outflow During Thiopental Anesthesia in Humans.” Anesth Analg 1990;71:319-26.
21. Aono H, Hirakawa M, Unruh GK, Kindscher JD, Goto H. “Anesthetic Induction Agents, Sympathetic Nerve Activity and Baroreflex Sensitivity: A Study in Rabbits Comparing Thiopental, Propofol and Etomidate.” Acta Med Okayama 2001;55:197-203.
22. Ebert TJ, Harkin CP, Muzi, M. “Cardiovascular Responses to Sevoflurane: A Review.” Anesth Analg 1995;81:S11-22.
23. Yamamura T, Kimura T, Furukawa K. “Effects of Halothane, Thiamylal, and Ketamine on Central Sympathetic and Vagal Tone.” Anesth Analg 1983;62:129-34.
24. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, Bodian CA. “Predictors of Hypotension After Induction of General Anesthesia.” Anesth Analg 2005;101:622-8.
25. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Gludicelli JF, Viars P. “Influence of Chronic Angiotensin-converting Enzyme Inhibition on Anesthetic Induction.” Anesthesiology 1994; 81:299-307.
26. Goldman L, Caldera DL. “Risks of General Anesthesia and Elective Operation in the Hypertensive Patient.” Anesthesiology 1979; 50:285-92.
27. Marty J, Gauzit R, Lefevre P, Couderc E, Farinotti R, Henzel C, Desmonts JM. “Effects of Diazepam and Midazolam on Baroreflex Control of Heart Rate and on Sympathetic Activity in Humans.” Anesth Analg 1986;65:113-9.
28. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. “Sympathetic Responses to Induction of Anesthesia in Humans with Propofol or Etomidate.” Anesthesiology 1992;76:725-33.
29. Ebert TJ, Muzi M, Lopatka CW. “Neurocirculatory Responses to Sevoflurane in Humans: A Comparison to Desflurane.” Anesthesiology 1995: 83;88-95.
30. Goldmann A, Hoehne C, Fritz GA, Unger J, Ahlers O, Nachtigall I, Boemke W. “Combined vs Isoflurane/Fentanyl anesthesia for major abdominal surgery: Effects

on hormones and hemodynamics." Med Sci Monit 2008;14:CR445-52.
31. Heyndrickx GR, Boettcher DH, Vatner SF. "Effects of angiotensin, vasopressin, and methoxamine on cardiac function and blood flow distribution in conscious dogs." Am J Physiol 1976;231:1579-87.
32. Brand PH, Metting PJ, Britton SL. "Support of arterial blood pressure by major pressor systems in conscious dogs." Am J Physiol 1988;255:H483-91.
33. Paller MS, Linas SL. "Role of angiotensin II, α-adrenergic system, and arginine vasopressin on arterial pressure in rat." Am J Physiol 1984;246:H25-30.
34. Carp H, Vadhera R, Jayaram A, Garvey D. "Endogenous Vasopressin and Renin-Angiotensin Systems Support Blood Pressure after Epidural Block in Humans." Anesthesiology 1994;80:1000-7; discussion 27A-28A
35. Clinical autonomic testing report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1996;46(3):873 -880
36. American Diabetes Association and American Academy of Neurology: Proceedings of a consensus development onference on standardized measures in diabetic neuropathy. *Diabetes Care* 1992;15:1080–1107
37. Keyl C, Lemberger P, Palitzsch KD, et al. Cardiovascular autonomic dysfunction and hemodynamic response to anesthetic induction in patients with coronary artery disease anddiabetes mellitus. Anesth Analg 1999;88:985-91.
38. Airaksinen KE, Niemelä MJ, Huikuri HV.Effect of beta-blockade on baroreflex sensitivity and cardiovascular autonomic function tests in patients with coronary artery disease Eur Heart J. 1994 Nov;15(11):1482-5.
39. Mirakhur A, Walshaw MJ. "Autonomic dysfunction in cystic fibrosis." J R Soc Med 2003;96 Suppl 43:11-7.
40. Szollosi I, King SJ, Wilson JW, Naughtun MT. "Tachycardia in adults with cystic fibrosis is associated with normal autonomic function." Intern Med J 2011;41:455-61.
41. Davis PB. "Physiologic Implications of the Autonomic Aberrations in Cystic Fibrosis." Horm Metab Res 1986;18:217-20.