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Hypercapnia during transcatheter aortic valve replacement under monitored anaesthesia care: a retrospective cohort study

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ABSTRACT

Background Acute intraoperative hypercapnia and respiratory acidosis, which can occur during monitored anaesthesia care (MAC), pose significant cardiopulmonary risks for patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR). The goal of the present study is to assess the incidence, risk factors and impact of intraoperative hypercapnia during MAC for patients undergoing transfemoral TAVR.

Methods Data was collected retrospectively from the electronic medical record of 201 consecutive patients with available intraoperative arterial blood gas (ABG) data who underwent percutaneous transfemoral TAVR with MAC using propofol and dexmedetomidine. ABGs (pH, arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen) were performed at the start of each case (baseline), immediately prior to valve deployment (ValveDepl), and on arrival to the postanaesthesia care unit. Data was analysed using Fisher's exact test, unpaired Student's t-test, Wilcoxon rank sum or univariate linear regression as appropriate based on $PaCO_2$ and pH during ValveDepl ($PaCO_2$-ValveDepl, pH-ValveDepl) and change in $PaCO_2$ and pH from baseline to ValveDepl ($PaCO_2$-%increase, pH-%decrease) to determine their association with preoperative demographic data, intraoperative anaesthetic and vasoactive medications and postoperative outcomes.

Results $PaCO_2$ increased by a mean of 28.4% and was higher than baseline in 91% of patients. Younger age, male sex, increased weight and increased propofol dose contributed to higher $PaCO_2$-ValveDepl and greater $PaCO_2$-%increase. Patients with $PaCO_2$-ValveDepl>60 mm Hg, pH≤7.2 and greater pH-%decrease were more likely to receive vasoactive medications, but perioperative $PaCO_2$ and pH were not associated with adverse postoperative outcomes.

Conclusions Transient significant hypercapnia commonly occurs during transfemoral TAVR with deep sedation using propofol and dexmedetomidine. Although the incidence of postoperative outcomes does not appear to be affected by hypercapnia, the need for vasopressors and inotropes is increased. If deep sedation is required for TAVR, hypercapnia and the need for haemodynamic and ventilatory support should be anticipated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Acute intraoperative hypercapnia can occur during monitored anaesthesia care (MAC) and may pose significant cardiopulmonary risk in patients undergoing transcatheter aortic valve replacement (TAVR), especially because patients with aortic stenosis and heart failure often present with underlying respiratory dysfunction and baseline hypercapnia.

WHAT THIS STUDY ADDS

⇒ Hypercapnia commonly occurs in patients undergoing TAVR with MAC and is associated with an increase in vasoactive medication use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Physicians providing sedation to patients undergoing TAVR must be aware of the possibility of severe hypercapnia in this patient population and should be prepared to administer haemodynamic and ventilatory support.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is a safe and effective treatment option for adults with severe symptomatic aortic stenosis (AS).[1 2] With the majority of TAVR now being performed via the percutaneous transfemoral approach,[3–5] anaesthetic choice has shifted from general anaesthesia (GA) to monitored anaesthesia care (MAC) and moderate sedation,[6–8] with reported benefits including improved haemodynamic stability, shorter procedure times, reduced hospital length of stay (LOS) and intensive care unit (ICU) LOS, faster recovery, decreased respiratory complications, reduced costs and reduced in-hospital and 30-day mortality.[6 9–16]

Sedation techniques during MAC vary, with anaesthetic depth ranging from minimal to deep sedation, the latter being similar to GA without controlled ventilation.[3 4 8 9 11 17–19]

Because many anaesthetic medications decrease central respiratory drive and cause upper airway obstruction, deeper sedation may lead to hypercapnia and other adverse respiratory events such as atelectasis, respiratory depression and subsequent oxygen desaturation and hypoxemia when compared with minimal or moderate sedation or GA with a secured airway and controlled ventilation.[11 20–25] While acute mild hypercapnia in the perioperative period is generally reversible and well tolerated,[26–28] severe hypercapnia in the presence of acidosis can be associated with cardiopulmonary and neurocognitive dysfunction.[29–33]

Patients with AS may present for TAVR with respiratory dysfunction, sleep disordered breathing and hypercapnia related to heart failure and pulmonary oedema.[34–36] They are also at risk for cardiovascular complications, especially those presenting with pulmonary hypertension,[37–43] and may be susceptible to the physiologic sequelae of hypercapnia, acidosis and hypoxemia.

The primary goal of the present study is to assess the incidence and risk factors of intraoperative hypercapnia in patients with AS undergoing transfemoral TAVR with MAC. Secondarily, the impact of hypercapnia on perioperative outcomes is analysed. We hypothesise that hypercapnia commonly occurs but is transient and does not impact postoperative outcomes.

METHODS

Study population

This retrospective cohort study included patients undergoing non-emergent percutaneous transfemoral TAVR under MAC with the Edwards Sapiens valve (Edwards Lifesciences, Irvine, California, USA) between 1 April 2019 and 31 March 2022. Patients without intraoperative arterial blood gas (ABG) data available in the electronic medical record (EMR) were excluded. Out of 655 patients who underwent percutaneous transfemoral TAVR during the study period, ABG data were available for 201 patients.

Anaesthetic conduct

The standard anaesthetic technique for TAVR at our institution is MAC. GA is reserved for patients with anticipated intolerance to sedative medications or for those undergoing alternative access TAVR. Routine clinical practice includes preoperative intravenous catheter placement, standard American Society of Anesthesiologists non-invasive monitoring, an arterial line for invasive blood pressure monitoring and the Bispectral Index Monitoring System (BIS, Medtronic, Minneapolis, Minnesota, USA) for depth of sedation monitoring. In addition, ABG analyses are performed regularly using the GEM Premier 4000 (Werfen, Bedford, Massachusetts, USA).

In the operating room, all patients receive supplemental oxygen (8 L/min) via non-rebreather facemask. Anaesthetic medications routinely administered include a combination of dexmedetomidine and propofol infusions titrated to optimise patient comfort, minimise patient movement and preserve spontaneous ventilation. Additional medications, including midazolam, fentanyl and ketamine, are administered at the discretion of the attending anaesthesiologist.

Intraoperative hemodynamics are managed by the anaesthesiologist using intravenous vasoactive medications as needed. Vasopressors include norepinephrine, phenylephrine and/or vasopressin. Inotropes include epinephrine administered to patients with severe myocardial dysfunction.

Post procedure, patients are either brought to the postanaesthesia care unit (PACU) or the Coronary Care Unit if they actively require infusions of vasoactive medications, transvenous pacing and/or if they experienced procedural complications.

Data

Data was collected retrospectively from the EMR of patients included in the study. Preoperative demographic data included age, sex, weight and body mass index (BMI). Baseline pulmonary data included the presence of chronic obstructive pulmonary disease (COPD), home oxygen requirement, obstructive sleep apnoea (OSA) and history of smoking (never, former or current). Additional preoperative end organ function data included renal glomerular filtration rate (GFR, mL/min), left ventricular ejection fraction (LVEF, %) and right ventricular systolic pressure (RVSP, mm Hg).

Analysed ABG data included the pH, arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2) at three time points: baseline, valve deployment (ValveDepl) and PACU. The baseline ABG was obtained prior to sedation while receiving supplemental oxygen. The next ABG was obtained intraoperatively after heparin administration and immediately prior to ValveDepl (pH, $PaCO_2$ and PaO_2-ValveDepl). The PACU ABG was performed in the immediate postoperative period on arrival to PACU before removing the non-rebreather facemask. The per cent increase in $PaCO_2$ from baseline to sedation ($PaCO_2$-%increase) and per cent decrease in pH from baseline to sedation (pH-%decrease) was calculated using the equations:

$$PaCO_2\%\text{increase} = \left(PaCO_2\text{ValveDepl} - PaCO_2\text{baseline}\right) \times 100 \div PaCO_2\text{baseline}$$

$$\text{pH}\%\text{decrease} = \left(\text{pHbaseline} - \text{pHValveDepl}\right) \times 100 \div \text{pHbaseline}$$

Intraoperative BIS data was recorded from the EMR at the ValveDepl time point.

Operating room time was defined as the length of time between arrival to the operating room and departure from the operating room.

Doses of midazolam, fentanyl and ketamine were recorded from the EMR. The total doses of propofol and dexmedetomidine administered were also recorded and then divided by patient weight and operating room time

to obtain an average administration rate over the duration of the case (µg/kg/min for propofol and µg/kg/hour for dexmedetomidine).

Vasoactive medications

Administration of vasopressors or inotropes during the case (any vs none) and just prior to ValveDepl (any vs none) was recorded. The total administered vasopressor and inotrope medication dose was measured in 'vasopressor equivalents' (µg) adapted from the equation described by Goradia *et al*[44]:

$$\text{Total vasopressor equivalents } (\mu g) = \text{norepinephrine } (\mu g) + \text{epinephrine } (\mu g) + \text{phenylephrine } (\mu g) \div 10 + \text{vasopressin (units)} \times 2.5$$

This was then divided by operating room time and patient weight to obtain average vasopressor equivalents (µg/kg/min) for the case duration.

Postoperative outcomes

Postoperative outcome variables included postprocedure hospital LOS, ICU LOS and 30-day mortality. Postoperative delirium, stroke and need for postoperative pacemaker insertion were also recorded.

Statistical analysis

The associations between $PaCO_2$-ValveDepl and $PaCO_2$-%increase and independent variables such as demographic data (age, sex, weight, BMI), end organ function (COPD, asthma, home O_2 dependence, smoking status, LVEF, RVSP, GFR), administered anaesthetic and vasoactive medications, BIS and postoperative outcome variables were analysed. The normal range for $PaCO_2$ is 35–45 mm Hg and a normal pH ranges between 7.35 and 7.45. Definitions of mild, moderate and severe hypercapnia vary and studies arbitrarily select $PaCO_2$ cut-offs for analyses. Mild-to-moderate elevations of $PaCO_2$ are described between 45 and 60 mm Hg, becoming severe with $PaCO_2$>60 mm Hg and pH<7.25.[26–28 30 45] Hypercapnic acidosis with $PaCO_2$>60 mm Hg and pH<7.20 is associated with worse outcomes.[29 30 45–47]

ABG data was therefore analysed based on $PaCO_2$-ValveDepl (≤60 mm Hg and >60 mm Hg), pH-ValveDepl (≤7.2 and >7.2) and $PaCO_2$-%increase (≤50% and >50%). Categorical variables were reported as counts and percentages and continuous variables as mean±SD. Categorical variables were analysed with Fisher's exact test. Continuous variables were analysed using unpaired Student's t-test or Wilcoxon rank sum (two group comparison) as appropriate after being assessed for normality. To assess the changes in $PaCO_2$, PaO_2 and pH over the course of the study (Baseline, ValveDepl, PACU), repeated measures generalised linear mixed models were used.

$PaCO_2$-ValveDepl, $PaCO_2$-%increase, pH-ValveDepl and pH-%decrease were also analysed as continuous variables using univariate regression models to examine their linear relationships with the above independent variables. This same analysis was repeated for RVSP groups of <40 mm Hg, 40–60 mm Hg and RVSP>60 mm Hg to analyse the effects of hypercapnia on outcomes in patients with pre-existing pulmonary hypertension.

In a series of separate analyses, to better elucidate the variables affecting vasopressor administration, univariate linear regression models were used to describe the linear relationship between infusion rates of propofol and dexmedetomidine and BIS and average vasopressor equivalents. Next, patients who were administered a vasopressor during the case were compared with those who did not using the methodology described above for two group comparisons. A similar analysis was conducted for administration of inotrope.

In addition, the linear relationships between the above independent variables and ICU LOS and postprocedure hospital LOS were analysed using univariate linear regression models, while the association between the above independent variables and need for ICU admission, postoperative delirium, stroke and need for postoperative pacemaker insertion were analysed using unpaired Student's t-test or Wilcoxon rank sum and Fisher's exact test.

A threshold of 0.05 was used for statistical significance in all analyses and p values were two sided. All statistical analyses were conducted with the use of SAS software V.9.4.

RESULTS

201 patients were included in the data analysis (dataset).[48] The mean age of the study population was approximately 79 years. Preoperative demographic data are found in table 1.

Medications

All but one patient received both propofol and dexmedetomidine infusions. The average propofol dose (µg/kg/min) was found to be inversely correlated with age (p=0.0037). 92 patients (45.8%) received 1–4 mg of midazolam, 59 (29.4%) received 25–100 µg of fentanyl and 7 (3.5%) received 25–100 mg ketamine injections. 91% (182/201) of all cases received a vasopressor at some point during the case.

The mean BIS at the time of ValveDepl was 48. In a univariate linear regression analysis, lower BIS was associated with higher total dose (p=0.009) and average infusion rate (p=0.0001) of propofol, as well as total midazolam dose (p=0.0047).

There were no significant linear associations between BIS or amount of dexmedetomidine or propofol administered and total or average vasopressor equivalents. Preoperative RVSP was not associated with the intraoperative administration of a vasoactive medication, while a reduced LVEF (40.0%±15.8% vs 59.2%±13.3%) was associated with more frequent inotrope use (p=0.002). Other predictors of inotrope use included longer procedure time (53.4 vs 38.4 min; p=0.03) and a longer operating room time (165.1 vs 125.8 min; p=0.005).

Table 1 Demographic data

Sex	
Female % (n)	40.3% (81)
Male % (n)	59.7% (120)
Age	
Mean±SD (range)	78.7±8.8 (49-100)
Body mass index	
Mean±SD (range)	29.0±5.3 (18.7–48.0)
Weight (kg)	
Mean±SD (range)	81.8±17.8 (43.5–147.4)
Chronic obstructive pulmonary disease	17.4% (35)
Asthma	13.9% (28)
Smoking status	
Never % (n)	37.8% (76)
Former % (n)	57.7% (116)
Current % (n)	4.5% (9)
Obstructive sleep apnoea % (n)	21.9% (44)
Home oxygen % (n)	2.5% (5)
Glomerular filtration rate (mL/min)	
Mean±SD (range)	54.7±10.0 (6-60)
Left ventricular ejection fraction (%)	
Mean±SD (range)	58.5±13.8 (10-80)
Right ventricular systolic pressure (mm Hg)	
Mean±SD (range)	37.6±12.8 (18-90)

ABG data

At the time of ValveDepl, the pH ranged from 7.15 to 7.52 and the $PaCO_2$ ranged from 30 to 100 mm Hg. 63% (126/201) of patients had a $PaCO_2$-ValveDepl>50 mm Hg and 26% (52/201) had a $PaCO_2$-ValveDepl>60 mm Hg. A pH<7.20 was recorded in 0.4% (n=7) of patients (table 2).

Seven patients did not have a baseline ABG available and were therefore excluded from analyses involving $PaCO_2$-%increase. $PaCO_2$-ValveDepl was higher than $PaCO_2$-baseline in 91% of patients. From baseline to the time of ValveDepl, the $PaCO_2$ increased by 28.4% and was associated with a fall in pH. Although the $PaCO_2$ decreased from ValveDepl by 19.8% on arrival to the PACU (p<0.0001), it remained greater than baseline (p=0.01). 15% (n=29) of patients recorded an increase of $PaCO_2$ of more than 50% at the time of ValveDepl compared with baseline.

PaO_2 increased from baseline to the time of ValveDepl and decreased in PACU. PaO_2 levels were not related to changes in $PaCO_2$.

Demographic data and ABG data

Table 3 summarises the ABG and BIS data at the time of sedation for $PaCO_2$-ValveDepl≤60 mm Hg vs >60 mm Hg, pH-ValveDepl<7.2 vs >7.2 and $PaCO_2$-%increase≤50% vs >50%. pH-ValveDepl and $PaCO_2$-ValveDepl were significantly different for each comparison (p<0.001).

Table 4 describes the correlation between preoperative demographic variables, organ function data and $PaCO_2$ and pH data. Male sex, younger age and increased weight were significantly associated with $PaCO_2$-ValveDepl>60 mm Hg. Univariate linear regression analyses showed statistically significant linear relationships between higher $PaCO_2$-ValveDepl with younger age (p=0.0025), greater BMI (p=0.0353) and weight (p=0.0052). There was a significant relationship between a larger $PaCO_2$-%increase and male sex (p=0.0003).

The presence of chronic lung diseases, such as COPD or asthma, home O_2 dependence, smoking status and OSA, was not associated with increased $PaCO_2$-ValveDepl, greater PaCO2-%increase, pH-ValveDepl or pH-%decrease.

Table 2 Summary of arterial blood gas data at baseline, at the time of valve deployment or in the postanaesthesia care unit (PACU)

	$PaCO_2$-baseline	$PaCO_2$-ValveDepl	$PaCO_2$-PACU
Mean±SD	42.5±6.5	54.6±10.6*	43.8±6.7†‡
Range	27–68	30–100	30–68
	pH-baseline	**pH-ValveDepl**	**pH-PACU**
Mean±SD	7.41±0.05	7.31±0.06*	7.37±0.04*‡
Range	7.27–7.52	7.15–7.52	7.23–7.52
	PaO_2-baseline	**PaO_2-ValveDepl**	**PaO_2-PACU**
Mean±SD	204.0±101.95	260.5±111.6*	145.8±73.1*‡
Range	(42–469)	(69–605)	(39–358)

*P<0.0001 compared with baseline.
†P<0.01 compared with baseline.
‡P<0.0001 compared with ValveDepl.
$PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; ValveDepl, valve deployment.

Table 3 Intraoperative arterial blood gas data

	$PaCO_2$-ValveDepl≤60 mm Hg (n=149)	$PaCO_2$-ValveDepl>60 mm Hg (n=52)	P value	$PaCO_2$-%increase<50% (n=165)	$PaCO_2$-%increase>50% (n=29)	P value	pH-ValveDepl>7.2 (n=194)	pH-ValveDepl≤7.2 (n=7)	P value
pH-ValveDepl Mean±SD (Range)	7.33±0.05 (7.20–7.52)	7.25±0.04 (7.15–7.33)	<0.001	7.32±0.06 (7.15–7.52)	7.25±0.05 (7.17–7.33)	<0.001	7.31±0.06 (7.21–7.52)	7.18±0.02 (7.15–7.20)	<0.001
$PaCO_2$-ValveDepl (mm Hg) Mean±SD (Range)	49.8±6.4 (30.0–60.0)	68.3±7.8 (61.0–100.0)	<0.001	53.0±9.8 (30.0–100.0)	63.2±10.0 (42.0–89.0)	<0.001	53.8±9.5 (30.0–84.0)	77.0±15.0 (56.0–100.0)	<0.001
PaO_2-ValveDepl (mm Hg) Mean±SD (Range)	261.3±103.5 (80.0–605.0)	258.0±133.5 (69.0–579)	0.875	269.5±105.3 (80.0–605.0)	225.6±141.1 (69.0–579)	0.120	261.9±111.2 (69.0–605.0)	213.7±123.2 (70.0–401.0)	0.298

Th compares $PaCO_2$-ValveDepl≤60 mm Hg and >60 mm Hg (201 total patients); $PaCO_2$-%increase from baseline of ≤50% and >50% (194 total patients); and pH-ValveDepl≤7.2 and >7.2 (201 total patients).
$PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; ValveDepl, valve deployment.

Medications and ABG data

Higher total and average propofol dose and lower BIS-ValveDepl were significantly associated with $PaCO_2$-ValveDepl>60 mm Hg, but not with $PaCO_2$-%increase>50% or pH-ValveDepl<7.2. Higher total (p<0.0001) and average (p<0.0001) propofol dose were also associated with higher $PaCO_2$-ValveDepl, greater $PaCO_2$-%increase and greater pH-%decrease in separate univariate linear regression analyses. Ketamine administration was significantly associated with $PaCO_2$-increase>50%, but was only administered to seven patients (table 5).

Both $PaCO_2$-%increase>50% and pH≤7.2 were significantly related to higher total and average vasopressor equivalents. Greater pH-%decrease was significantly associated with more frequent administration of a vasopressor at the time of ValveDepl (p=0.0016), as well as higher total (p=0.0388) and average (p=0.0085) vasopressor equivalents. Patients who received a vasopressor during the case had a higher $PaCO_2$-ValveDepl (55.2±10.6 vs 48.2±9.0; p=0.006), higher $PaCO_2$-%increase (30.6% vs 18%; p=0.03), lower pH-ValveDepl (7.30±0.06 vs 7.36±0.07; p=0.002) and greater pH-%decrease (1.4% vs 0.7%; p=0.024) than those who did not.

Administration of inotropes was more likely in patients with $PaCO_2$-ValveDepl>60 mm Hg and $PaCO_2$-%increase>50%. The average $PaCO_2$-%increase for patients receiving an inotrope was 55.8% compared with a 28.5% for those who did not receive an inotrope (p=0.002), while the average pH-%decrease for those receiving an inotrope was 2.1% compared with a 1.3% for those who did not receive an inotrope (p=0.008).

Outcomes

There was one death (0.5%) at 30 days post TAVR. Two patients suffered a stroke (1%). Six patients (3%) were diagnosed with postprocedure delirium. 11 patients (5.5%) required a pacemaker postoperatively. 35 patients (17.4%) were admitted to the ICU with a mean ICU LOS of 2.5±1.6 days. The mean hospital LOS for the total group was 1.8 days (±1.9 days). Patients admitted to the ICU had a longer hospital LOS (4.3 vs 1.3 days; p<0.001).

25 patients (12.4%) were readmitted to the hospital within 30 days.

A higher likelihood of ICU admission was related to lower average propofol doses (33.6 vs 42.1 µg/kg/min; p<0.005), higher BIS (52.2 vs 46.7; p=0.04), older age (82 vs 78 years; p<0.0001) and greater total (528.6 vs 203.8 µg; p<0.001) and average vasopressor equivalents (0.04 vs 0.02 µg/kg/min; p<0.001). ICU admission was more frequent in patients who required a longer procedure (47.6 vs 37.1 min; p=0.013) and operating room time (156.8 vs 120.9 min; p<0.001). Patients who received inotropes required a longer ICU LOS compared with those who did not (3.0±2.8 vs 0.4±0.9 days; p<0.001).

Hospital LOS was longer in patients who were older (p=0.0139), had a lower GFR (p=0.0061), received higher total and average vasopressor equivalents (p<0.001), required an inotrope (p=0.03) and underwent a longer

Table 4 Preoperative patient demographic and organ function data

	$PaCO_2$-ValveDepl≤60 mm Hg (n=149)	$PaCO_2$-ValveDepl>60 mm Hg (n=52)	P value	$PaCO_2$-%increase<50% (n=165)	$PaCO_2$-%increase>50% (n=29)	P value	pH-ValveDepl> 7.2 (n=194)	pH-ValveDepl ≤ 7.2 (n=7)	P value
Sex (%)									
Female/male	45.6/54.4	25.0/75.0	0.009	43.6/56.4	24.1/75.9	0.064	40.7/59.3	28.6/71.4	0.704
Age (years)									
Mean±SD (range)	79.7±8.5 (57.0–100.0)	75.9±9.1 (49.0–92.0)	0.007	79.2±8.6 (49.0–100.0)	76.9±9.0 (60-91)	0.183	78.9±8.8 (49.0–100.0)	75.0±8.8 (66.0–91.0)	0.253
BMI (kg/m^2)									
Mean±SD (range)	28.6±5.0 (18.7–42.6)	30.2±5.9 (22.1–48.0)	0.094	29.1±5.2 (18.7–42.9)	28.2±6.0 (22.0–48.0)	0.205	29.0±5.3 (18.7–48.0)	27.7±4.4 (23.0–36.3)	0.515
Weight (kg)									
Mean±SD (range)	79.7±16.6 (43.5–136.1)	87.8±19.9 (56.7–147.0)	0.019	81.9±17.9 (43.5–147.4)	80.4±17.0 (59.0–127.0)	0.520	81.9±17.9 (43.5–147.4)	80.3±16.7 (64.9–111.6)	0.736
COPD%	17.5	17.3	1.000	17.6	13.8	0.791	17.0	28.6	0.351
Asthma%	15.4	9.6	0.359	14.6	3.5	0.135	13.9	14.3	1.000
Smoking status%									
Never/previous/current	40.3/55.7/4.0	30.8/63.5/5.8	0.439	39.4/55.8/4.8	31.0/65.5/3.5	0.691	37.6/58.2/4.1	42.9/42.9/14.3	0.284
OSA%	19.5	28.9	0.175	21.2	24.1	0.807	22.7	0.0	0.351
Home O_2%	2.0	3.9	0.606	3.0	0.0	1.000	2.6	0.0	1.000
GFR									
Mean (mL/min) ±SD (range)	54.3±10.1 (6.0–60.0)	56.0±10.0 (12.0–60.0)	0.039	54.8±9.6 (12.0–60.0)	56.9±8.5 (26.0–60.0)	0.081	54.7±10.1 (6.0–60.0)	56.9±8.3 (38.0–60.0)	0.302
LVEF									
Mean (%)±SD (range)	59.7±13.2 (10.0–80.0)	55.1±14.8 (15.0–80.0)	0.054	58.7±13.7 (12.0–60.0)	57.7±15.0 (15.0–75.0)	0.798	58.4±13.9 (10.0–80.0)	60.7±8.4 (55.0–75.0)	0.875
RVSP									
Mean (mm Hg)±SD (range)	37.6±13.4 (18.0–90.0)	37.7±11.1 (19.0–66.0)	0.720	36.5±12.5 (18.0–90.0)	39.9±11.0 (24.0–67.0)	0.092	37.5±13.1 (18.0–90.0)	41.0±5.4 (36.0–51.0)	0.119

This compares $PaCO_2$-sedation≤60 mm Hg and >60 mm Hg (201 total patients); $PaCO_2$-%increase from baseline of ≤50% and >50% (194 total patients); and pH≤7.2 and >7.2 (201 total patients).
COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnoea; RVSP, right ventricular systolic pressure.

Table 5 Intraoperative anaesthetic (including BIS-ValveDepl) and vasoactive medications

	$PaCO_2$-ValveDepl≤60 mm Hg (n=149)	$PaCO_2$-ValveDepl>60 mm Hg (n=52)	P value	$PaCO_2$-%increase<50% (n=165)	$PaCO_2$-%increase>50% (n=29)	P value	pH-ValveDepl>7.2	pH-ValveDepl≤7.2	P value
Dexmedetomidine									
Total (µg)±SD (range)	115.4±50.6 (16.0–374)	123.7±61.1 (0.0–342.0)	0.561	118.0±51.6 (16.0–374.0)	115.5±61.9 (0.0–342)	0.428	118.2±53.1 (0.0–374.0)	98.4±65.7 (38.0–241.0)	0.076
Avg (µg/kg/hour)±SD (range)	0.28±0.12 (0.08–1.30)	0.27±0.07 (0.06–0.42)	0.949	0.28±0.12 (0.08–1.30)	0.27±0.07 (0.06–0.39)	0.964	0.28±0.11 (0.06–1.30)	0.24±0.07 (0.13–0.33)	0.384
Propofol									
Total (µg)±SD (range)	376.2±201.3 (0.0–1162.0)	521.6±332.4 (164.0–1960.0)	0.004	401.4±228.6 (0.0–1600.0)	498.0±352.2 (186.0–1860.0)	0.332	405.3±229.9 (0.0–1600.0)	649.3±567.8 (202.0–1860.0	0.217
Avg (µg/kg/min)±SD (range)	38.4±18.7 (0.78–94.2)	47.2±21.7 (12.1–114.4)	0.005	39.7±18.7 (0.8–94.2)	47.8±25.6 (12.1–114.4)	0.115	39.8±18.8 (0.78–94.2)	63.9±33.4 (27.0–114.4)	0.105
Fentanyl (any) %	27.5	34.6	0.378	29.1	31.0	0.828	28.9	42.9	0.421
Ketamine (any) %	4.7	0.0	0.194	1.2	13.8	0.005	3.6	0.0	1.000
BIS-ValveDepl									
Mean±SD (range)	49.0±13.5 (41–54)	43.7±10.7 (37–50)	0.036	48.6±13.3 (41–54)	44.7±10.9 (39–50)	0.304	47.7±13.2 (41–53)	47.4±10.0 (38–53)	0.909
Vasopressors									
Any during case %	88.6	96.2	0.167	90.3	96.5	0.477	90.2	100	1.000
Any at ValveDepl %	77.8	86.5	0.227	79.4	93.1	0.118	79.4	100	0.349
Vasopressor equivalents									
Total (µg)±SD (range)	246.4±271.9 (0.0–1932.0)	300.5±289.6 (0.0–1244.0)	0.180	234.5±260.0 (0.0–1932.0)	411.7±332.1 (0.0–1244.0)	0.002	256.3±279.4 (0.0–1932)	373.1±168.5 (134.0–695.5)	0.042
Avg (µg/kg/min)±SD (range)	0.024±0.026 (0.00–0.128)	0.028±0.024 (0.00–0.081)	0.247	0.023±0.024 (0.0–0.13)	0.038±0.027 (0.0–0.09)	0.002	0.025±0.025 (0.00–0.13)	0.043±0.021 (0.02–0.08)	0.020
Inotropes (any) (%)	1.3	9.6	0.013	1.2	17.2	<0.001	3.6	0.0	1.000

This compares $PaCO_2$-sedation≤60 mm Hg and>60 mm Hg (201 total patients); $PaCO_2$-%increase from baseline of ≤50% and >50% (194 total patients); and pH≤7.2 and >7.2 (201 total patients). Medications are recorded as either 'any' (% of patients), total dose or average dose per kilogram during the case (µg/kg/hour or µg/kg/min).
BIS, Bispectral Index Monitoring System; $PaCO_2$, arterial partial pressure of carbon dioxide; ValveDepl, valve deployment.

procedure (p<0.0001). Patients who experienced delirium had longer hospital LOS (p<0.0001).

Outcomes shown in table 6 were not related to $PaCO_2$-ValveDepl, $PaCO_2$-%increase or pH-ValveDepl. This did not change when these analyses were performed based on RVSP of <40 (mean 30.3±5.7) mm Hg, 40–60 (mean 46.7±5.1) mm Hg and >60 (mean 71.0±8.5) mm Hg.

DISCUSSION

Acute intraoperative hypercapnia is common in patients undergoing TAVR under MAC with deep sedation using propofol/dexmedetomidine. Compared with baseline, the $PaCO_2$ increased by an average of 28.4% at the time of ValveDepl, at which time 63% of patients recorded a $PaCO_2$>50 mm Hg and 26% (52/201) had a $PaCO_2$>60 mm Hg.

Patients with AS and heart failure undergoing TAVR are at an increased risk of baseline respiratory dysfunction and hypercapnia.[34–36] This risk may worsen during the perioperative period. In the present study, intraoperative hypercapnia was associated with higher propofol dose and lower BIS, as well as male sex and increased patient weight. Younger age, which was associated with greater propofol use, was also associated with hypercapnia, but the presence of COPD, asthma, home oxygen dependence, smoking history and OSA was not.

Despite the high incidence of hypercapnia, adverse outcomes in the present study compared favourably with the literature with lower rates of delirium, stroke and 30-day mortality, but there was an increased use of vasoactive medications.[6 8 12–16 18 49] Increased need for haemodynamic support was more likely with increased $PaCO_2$-ValveDepl, increased $PaCO_2$-%increase and decreased pH-ValveDepl and was associated with prolonged ICU and hospital LOS. However, $PaCO_2$-ValveDepl, $PaCO_2$-%increase, and pH-ValveDepl were not directly related to ICU admission, ICU and hospital LOS, or other adverse outcomes measured in this study. ICU admission and longer ICU and hospital LOS were instead more likely in older patients with reduced GFR who received less anaesthetic and in those who required longer procedure and operating room times.

These findings reflect the transient nature of anaesthetic effects and variation of anaesthetic technique depending on age and patient comorbidities and suggest that outcomes depended more on patient and procedural factors than anaesthetic management. In addition, permissive mild or moderate hypercapnia is associated with less inflammation and pulmonary tissue oedema, as well as increased bronchodilation and improved lung compliance.[45 46 50] Hypercapnia below 60 mm Hg is also reported to improve cardiac performance and mixed venous oxygen saturation.[51] Therefore, the absence of a relationship between hypercapnia and adverse outcomes might reflect the differential effects of mild or moderate hypercapnia versus severe hypercapnia and acidosis.

Table 6 Postoperative outcomes

	$PaCO_2$-ValveDepl≤60 mm Hg (n=149)	$PaCO_2$-ValveDepl>60 mm Hg (n=52)	P value	$PaCO_2$-%increase<50% (n=165)	$PaCO_2$-%increase>50% (n=29)	P value	pH-ValveDepl> 7.2	pH-ValveDepl≤7.2	P value
Admitted to ICU %	16.1	21.1	0.403	16.3	27.6	0.188	17.5	14.3	1.000
ICU LOS									
Mean (days)±SD (range)	0.4±1.2 (0.0–8.0)	0.49±1.82 (1.0–2.0)	0.441	0.4±1.1	0.7±1.3	0.162	0.45±1.2	0.14±0.4	0.734
Hospital LOS									
Mean (days)±SD (range)	1.8±2.0 (1.0–16.0)	1.9±1.8 (1.0–8.0)	0.738	1.9±2.0 (1.0–16.0)	1.8±1.7 (1.0–5.0)	0.732	1.8±2.0	1.3±0.5	0.767
Pacemaker %	5.4	5.8	1.000	5.5	6.9	0.671	5.7	0.0	1.000
30 day readmit %	12.1	13.5	0.809	12.7	10.3	1.000	12.9	0.0	0.600
30 day mortality %	0.0	1.9	0.259	0.6	0.0	1.000	0.5	0.0	1.000
Stroke %	1.3	0.0	1.000	1.2	0.0	1.000	1.0	0.0	1.000
Delirium %	2.0	5.8	0.181	3.6	0.0	0.594	3.1	0.0	1.000

This compares $PaCO_2$-sedation≤60 mm Hg and >60 mm Hg (201 total patients); $PaCO_2$-%increase from baseline of ≤50% and >50% (194 total patients); and pH≤7.2 and >7.2 (201 total patients).
ICU, intensive care unit; LOS, length of stay; $PaCO_2$, arterial partial pressure of carbon dioxide; ValveDepl, valve deployment.

Hypotension and the use of vasoactive medications during TAVR are dictated by baseline cardiovascular function, procedural events and anaesthetic effects. In general, haemodynamic perturbations during MAC are reported to be less compared with GA, with more frequent administration of vasopressors and inotropes with GA (84%–97%) versus MAC (48%–68%).[12–14 23 49] In the present study, administration rates of vasopressors and inotropes were closer to those reported for GA than MAC. This could be explained by lower BIS values (median of 46), which were consistent with a range recommended for GA or deep sedation[52–54] and were generally lower than BIS reported by other studies.[13 23 49] However, neither decreased BIS nor higher doses of propofol and dexmedetomidine were associated with an increase in vasoactive medication administration. Therefore, even when considering the deeper sedation provided in the present study, there was an independent effect of $PaCO_2$ and pH on administration of vasoactive medications that was not related to anaesthetic medications or BIS.

Few studies have reported an association between hypercapnia and haemodynamic effects during MAC. In a prospective study of 110 patients undergoing cardiac ablation under MAC/sedation, hypercapnic patients did not have a higher incidence of hypotension, though only 5 patients experienced a $PaCO_2$ greater than 70 mm Hg.[22] The authors did not analyse the effect of changes in $PaCO_2$ from baseline. In a small, randomised study comparing GA and MAC, MAC was associated with hypercapnia (50–60 mm Hg) but appeared to have no impact on haemodynamics or vasoactive medication use.[23] However, the authors did not specifically evaluate the impact of hypercapnia nor analyse the causes of hypotension. The same group later compared 141 patients who received a combination of propofol and opioid to 157 patients who received dexmedetomidine.[55] The propofol/opioid group experienced more hypercapnia (42% vs 25%) and were more likely to receive vasoactive medications (68% vs 25%). However, the analysis did not determine whether $PaCO_2$ was related to administration of vasoactive medications.

The effect of hypercapnic acidosis on cardiac function is phasic. While acidosis directly causes myocardial depression and vascular dilation, moderate hypercapnia increases sympathoadrenal activity and catecholamine synthesis, leading to increased heart rate, cardiac contractility and stroke volume and reduced systemic vascular resistance.[29 30 56–68] With more severe hypercapnia ($PaCO_2$>60 mm Hg) and acidosis (pH<7.2), myocardial depression dominates.[30 33 62 68] In a dog model, this phasic change was demonstrated with progressively increasing $PaCO_2$, which was initially accompanied by hypertension but progressed to hypotension with more severe hypercapnia and acidosis.[66] The sympathetic response to hypercapnia can also be attenuated by the effects of anaesthetic medications, which unmask the myocardial depressant effects of hypercapnic acidosis.[62 67]

Hypercapnia increases pulmonary vascular resistance and can cause subsequent right ventricular failure, particularly in patients who already have pulmonary hypertension.[56 57 61 62 65 69–72] Hypercapnia also potentiates regional hypoxic pulmonary vasoconstriction caused by atelectasis, which occurs in up to 90% of patients receiving anaesthesia,[50 60 73] further increasing right ventricular afterload.

This study is unique as it reports a high incidence of hypercapnia and associated haemodynamic effects during TAVR with MAC. While there was not a significant relationship between anaesthetic medications and vasoactive medications, the potential cardiovascular impact of anaesthetic medications cannot be minimised. Nonetheless, any haemodynamic instability related to hypercapnia is particularly concerning for patients with AS, many of whom present with preprocedure pulmonary hypertension.[37–43 74]

Postoperative pulmonary complications occur in <5% of TAVR cases, being greater in patients undergoing GA.[49 75 76] Intraoperative respiratory events, however, occur in more than 50% of patients undergoing TAVR with MAC.[23 55] The anaesthetic medications administered during MAC can cause intraoperative respiratory depression, which presents as atelectasis, hypoxemia, hypercapnia and a more frequent need for airway support.[11 19 23–25 55 77] In a randomised study comparing GA to MAC using propofol and remifentanil, airway and pulmonary complications occurred in 94% of the MAC patients compared with 13% of GA.[23] These included bradypnea, hypoxemia and the need for airway manipulation and bag mask ventilation. In a dose-dependent effect, propofol depresses the hypoxemic and hypercapnic ventilatory responses by inhibiting the response of central chemoreceptors to changes in $PaCO_2$.[78–80] This effect disappears within 30 min after discontinuation of the propofol infusion.[78–81] An association between hypercapnia and male sex in the present study may be explained by an increased sensitivity to propofol in men; however, men also have a stronger ventilatory response to CO_2.[82] Dexmedetomidine can cause upper airway obstruction and reduce the ventilatory response to hypoxemia and hypercapnia.[83] In the present study, use of higher doses of propofol but not dexmedetomidine was predictive of hypercapnia. Surprisingly, ketamine administration was more common in patients with a $PaCO_2$-%increase>50%. Although ketamine is not considered a respiratory depressant, a rapid injection may cause transient apnoea.[84 85] Conversion from MAC to GA occurs in up to 17% of cases.[11] Although conversion to GA is more commonly related to procedural complications and haemodynamic instability,[11 12 15 18 49] poor gas exchange and need to improve airway patency may also necessitate prompt conversion to GA.[23 77]

In the present study, a significant reduction in PaO_2 compared with baseline was reported in the PACU, while hypercapnia improved after the discontinuation of sedating medications. Perioperative atelectasis results in

regional hypoxia and hypoxic pulmonary vasoconstriction, which optimises ventilation–perfusion matching by reducing pulmonary blood flow to poorly oxygenated regions.[50 60 73] Hypercapnia related pulmonary vascular constriction enhances hypoxic pulmonary vasoconstriction, further minimising shunt.[50] Theoretically, with reduced sedation and improved ventilation, the reduction of hypercapnia and loss of enhanced hypoxic pulmonary vasoconstriction in the presence of persistent atelectasis could contribute to ventilation–perfusion mismatch, shunt and a lower PaO_2.[50]

Limitations

This was a retrospective study that relied on the EMR and was therefore limited by the accuracy and completeness of the data found in the charts. In addition, medication data collected was an aggregate of doses given over the entirety of each case, whereas $PaCO_2$ was measured at discrete times. Finally, anaesthetic technique was not controlled and led to variability in the use of sedative medications and deployment of airway adjuncts that may have affected our results.

Our study was not powered to find an association to find an association between intraoperative hypercapnia and postoperative outcomes. The observed outcome rates in our patient population were very low and a significantly larger number of patients would have been needed. We surmise that while hypercapnia may have exerted an effect on intraoperative haemodynamics, its effect on postoperative outcomes was likely small compared with the effect of patient comorbidities and procedural complications.

CONCLUSION

Severe hypercapnia occurs frequently and increases the need for vasoactive medications during TAVR with deep sedation using propofol and dexmedetomidine. This haemodynamic effect appears to be independent of anaesthetic depth. Outcomes, however, are not affected by transient hypercapnia as long as cardiopulmonary function is maintained. Adverse outcomes instead were more likely in older patients who received less anaesthetic and consequently experienced less hypercapnia and patients undergoing longer procedures.

MAC has become a popular anaesthetic for percutaneous transfemoral TAVR. Deep sedation may provide optimal operating conditions, but due to its potential cardiopulmonary effects, local anaesthesia with minimal or moderate sedation may be preferred in many patients. While future studies performing a controlled comparison of anaesthetic techniques may help better delineate the optimal anaesthetic for this patient population, anaesthetic technique should be tailored to fit each patient. If deep sedation is required to minimise patient motion, then hypercapnia and the need for haemodynamic and ventilatory support should be anticipated.

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