

Incidence of Propofol Infusion Syndrome during Noninvasive Radiofrequency Ablation for Atrial Flutter or Fibrillation

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Background: Propofol infusion syndrome is first manifest by unexplained metabolic acidosis. Its incidence is unknown.

Methods: Charts of all patients undergoing nonsurgical, catheter radiofrequency ablation for atrial flutter or fibrillation from 1999 through 2001 at Mayo Clinic Rochester, who received propofol and had an arterial blood gas drawn during the procedure, were reviewed retrospectively for metabolic acidosis, prospectively defined as base excess -2 or less. Of 301 radiofrequency ablation cases, 55 had an arterial blood gas. Virtually all radiofrequency ablation patients received propofol, so they could not be used as nonpropofol controls. Instead, all carotid endarterectomy patients in 2000 who did not receive propofol and had an arterial blood gas drawn after anesthetic induction and before surgical incision were used as a comparator group.

Results: In propofol radiofrequency ablation patients with no apparent cause of metabolic acidosis besides propofol, 13 of 55 (24%) had base excess of -2 or less, versus 22 of 267 carotid patients (8.2%) ($P < 0.01$). Maximal negative base excess was -4.2 ± 1.7 in these propofol patients and was not correlated with propofol dose, age, or fluid dose, versus base excess of -3.2 ± 1.5 in carotid patients ($P > 0.05$). Propofol patients received prolonged anesthetics (7 h) and high-dose propofol (20 mg/kg).

Conclusions: This is the first incidence estimate of metabolic acidosis during prolonged propofol infusion and suggests that it is not rare. The study is limited by its retrospective nature and by the lack of baseline arterial blood gas data and will require confirmation by prospective study.

PROLONGED infusion of propofol at a high dose has been associated with "propofol infusion syndrome," an otherwise unexplained metabolic acidosis sometimes associated with myocardial dysfunction or rhabdomyolysis. The syndrome occurs unpredictably by an unknown mechanism, and until recently was reported only in critically ill patients and was frequently fatal.¹⁻¹¹ Recent case reports,¹²⁻¹⁵ however, document the occurrence of reversible metabolic acidosis in non-critically ill patients receiving propofol, temporally related to propofol infu-

sion. Because otherwise unexplained metabolic acidosis temporally related to propofol is usually the initial indicator of the syndrome, regardless of mortality, and because the mechanism of propofol infusion syndrome has not yet been determined, we here use the term *propofol infusion syndrome* to include nonfatal cases where the primary indication is metabolic acidosis. There are a number of case reports where the only manifestation of propofol infusion syndrome was reversible metabolic acidosis.^{12,14-17} Although case reports have established the existence of propofol infusion syndrome and suggested that it is associated with prolonged infusion of high-dose propofol, its incidence is still unknown. There is no information as to whether the cases reported are extremely rare, idiosyncratic drug reactions or whether they are extreme manifestations of a more common syndrome that is usually overlooked because it is initially reversible and usually benign.

Propofol is frequently used to provide deep sedation for catheter-based radiofrequency ablation (RFA) of arrhythmic foci. Because the ablations can be prolonged and require periods with a motionless patient, arterial blood gases (ABGs) are often obtained at our institution at the cardiologist's and anesthesiologist's discretion to assess respiratory depression. These case records thus provide an opportunity to study the incidence of metabolic acidosis in patients with minimal surgical trauma, who received propofol at relatively high doses for many hours.

Materials and Methods

This retrospective chart review study was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota). Exclusion criteria for all cases were lack of patient consent for chart review for research purposes, missing or incomplete medical record, or the same procedure performed previously during the study period (so that only one anesthetic record per patient was studied). Patient records of all cases of RFA for atrial fibrillation or atrial flutter at Mayo Clinic Rochester from 1999 through 2001 were retrospectively examined. RFAs were studied because during that time, due to cardiologist preference and perceived less interference with electrophysiologic mapping, the majority of these patients received prolonged propofol infusion without initial intubation. Medical records of 302 patients were initially identified as nonexcluded and then screened for two inclusion criteria, receiving propofol (301 cases) and having an ABG

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drawn during the RFA, yielding 55 cases. None had a preanesthetic ABG. These records were then reviewed for the development of metabolic acidosis during the RFA, prospectively defined as a base excess (BE) of -2 or less. Although severe cases of propofol infusion syndrome cause a greater negative BE, our goal was to detect early or mild cases as well, if such occurred. In many published case reports, the early changes in BE before clinical manifestations are not reported, but in three well-documented cases of the syndrome, the initial negative BE was -2 to -3 .^{12,13,15}

Patients who showed a metabolic acidosis with propofol had their complete medical records reviewed to determine which anesthetic agents were used, all ABGs and times drawn, the total dose of propofol given, the average and maximal rate of propofol infusion, time from first to last dose of propofol, adverse outcomes after the procedure and their relation to acidosis, and possible causes of metabolic acidosis besides propofol. Prospectively defined alternate causes were cardiac dysfunction other than arrhythmia (valvular disease, evidence of ischemia or infarction, intracardiac shunts, or left ventricular ejection fraction $< 40\%$), diabetes mellitus, renal disease with creatinine > 2.0 , hypoxemia (pulse oximeter or arterial blood gas oxygen saturation $\leq 96\%$ at any time during the RFA), hypotension (systolic blood pressure ≤ 90 mmHg for 15 or more consecutive minutes), or anemia with hemoglobin < 10.0 g/dl. Cases of metabolic acidosis without an alternate nonpropofol cause were also reviewed for type of intravenous fluid given, its volume, and the time over which it was given.

We were unable to use RFA patients as controls not receiving propofol, as originally planned, because in this patient population virtually every patient received propofol. Instead, after the analysis of the RFA group was performed, all patients undergoing carotid endarterectomy (CEA) at Mayo Clinic Rochester during 2000 were used as a comparator population, because most of them had a baseline ABG drawn before surgical stress and few received propofol. CEA patients were excluded if they received propofol before their ABG. Baseline BE values were then recorded for the 267 nonexcluded CEA patients who had an ABG drawn after anesthetic induction and before surgery.

Statistical Analysis

Comparison of the number of metabolic acidosis patients in propofol RFA and CEA groups was performed by chi-square analysis with the Fisher exact test. Similar comparisons using the subgroups of propofol RFA patients with and without nonpropofol factors contributing to metabolic acidosis were performed by the same method and then adjusted with the Bonferroni correction for multiple comparisons. The 95% confidence interval for the incidence of metabolic acidosis in patient populations was determined using the adjusted Wald method.¹⁸ Other data are presented as mean \pm SD. For

quantitative analysis of the magnitude of metabolic acidosis in RFA propofol patients, the maximal negative BE during the anesthetic was analyzed. Comparison of a single continuous variable between two groups was by two-tailed *t* test. The relation of maximal negative BE to propofol dose for RFA patients, of age to initial BE for CEA patients, and of fluid administration rate to BE for RFA patients was determined by linear correlation analysis and quantified by the Pearson product-moment correlation coefficient (*R*) as well as significance. Statistical calculations were performed using the algorithms in Systat 7.0 (Systat Software Inc., Richmond, CA).

Results

Metabolic Acidosis in Patients with and without Propofol Treatment

The incidence of metabolic acidosis in the two study populations is summarized in table 1. Of the nonpropofol CEA patient comparator group, 22 of 267 (8.2%) had a metabolic acidosis (BE ≤ -2). Of the propofol RFA patients, 50 of 55 (91%) had at least one ABG documenting metabolic acidosis. Of these, 13 (24% of 55; 95% confidence interval, 14–36%) seemed to have no other potential cause of metabolic acidosis than propofol, using the criteria established prospectively ($P < 0.01$ compared with nonpropofol). The difference in incidence of metabolic acidosis in propofol groups with or without other apparent causes of metabolic acidosis, compared with the CEA comparator group, was highly significant ($P < 0.01$). The magnitude of the maximal negative BE was -4.2 ± 1.7 for propofol patients with no other apparent cause of metabolic acidosis and -5.4 ± 2.4 for propofol patients with other possible causes of metabolic acidosis, versus -3.2 ± 1.5 for baseline BE in CEA. The only significant difference in BE magnitude was CEA versus propofol with other causes ($P < 0.01$).

No adverse outcomes were attributable to metabolic acidosis in the RFA propofol study population. Postprocedure ABGs were generally not tested because the patients were completely recovered from the anesthetic without clinically apparent sequelae.

Subgroup Analysis of Propofol Patients with Metabolic Acidosis

Table 2 summarizes the characteristics of the metabolic acidosis propofol patients with and without nonpropofol causes of metabolic acidosis. There was little significant difference in patient characteristics between the two groups. Both groups received prolonged anesthetics and high-dose propofol. Although the average rate of approximately $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is lower than in most reported cases of propofol infusion syndrome, it is consistent with the lesser degree of metabolic acidosis in our patients compared with reported cases with the

Table 1. Incidence of Metabolic Acidosis without and with Propofol

Without Propofol	With Propofol
293 carotid endarterectomy cases without propofol	301 radiofrequency ablation cases with propofol
↓	↓
267 with baseline ABG	55 with ABG during case
↓	↓
22 with metabolic acidosis Incidence = 22/267 = 8.2%*† 95% CI = 5.5–12%	50 with metabolic acidosis Incidence = 50/55 = 91%*† 95% CI = 80–96%
	↓
	37 with other potential causes‡ of metabolic acidosis besides propofol Incidence = 37/55 = 67%*§ 95% CI = 54–78%
	↓
	13 with propofol only apparent cause of metabolic acidosis Incidence = 13/55 = 24%*§ 95% CI = 14–36%

* Incidence and 95% confidence interval (CI) are with reference to those patients in each group with an arterial blood gas (ABG). † $P < 0.001$, without vs. with propofol. ‡ Cardiac dysfunction other than arrhythmia (valvular disease, evidence of ischemia or infarction, intracardiac shunts, or left ventricular ejection fraction $< 40\%$), diabetes mellitus, renal disease with creatinine > 2.0 , hypoxemia (arterial oxygen saturation or pulse oximeter $\leq 96\%$ at any time during the radiofrequency ablation), hypotension (systolic blood pressure ≤ 90 mmHg for 15 or more consecutive minutes), or anemia with hemoglobin < 10.0 g/dl. § $P < 0.01$ for comparison of metabolic acidosis incidence in either propofol acidosis subgroup with the without-propofol comparator group.

fulminant syndrome. Also, a propofol infusion rate ($32 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) similar to that in our patients has recently been reported in a patient with severe, fatal propofol infusion syndrome.¹⁹

The distribution of BE values for all metabolic acidosis patients receiving propofol is shown in figure 1 (y-axis). There was no correlation between maximal negative BE and propofol dose in patients with or without other potential nonpropofol causes of metabolic acidosis, whether the propofol dose was analyzed as average infusion rate, maximal infusion rate, total dose (mg/kg), or time receiving propofol (hours).

Other than propofol, none of drugs received by the 13 patients without apparent cause of metabolic acidosis (fentanyl $n = 11$, midazolam $n = 10$, succinylcholine $n = 5$, diazepam $n = 2$, and isoproterenol $n = 11$ [used to facilitate electrophysiologic mapping, not to support circulation]) are likely to be causes of metabolic acidosis.

Potential Confounding Factors

The ages of the propofol RFA patients (55 ± 13 yr) differed significantly from the ages of the nonpropofol CEA patients (71 ± 9 yr). However, correlation analysis of the ages of CEA patients and their BEs showed no

significant association ($R^2 = 0.0004$, $P = 0.73$), suggesting that the difference in ages between the two study populations should not confound the comparison between BEs of the populations.

Intravenous infusion of large amounts of 0.9% sodium chloride has been implicated as a cause of metabolic acidosis.^{20,21} Of the 13 patients without other apparent nonpropofol causes of metabolic acidosis, 11 received 0.9% sodium chloride as their intravenous fluid, at an average rate of 459 ± 227 ml/h. Correlation analysis found no relation between the rate of fluid administration and maximal negative BE for these 11 patients ($R^2 = 0.03$, $P = 0.62$), suggesting that 0.9% sodium chloride cannot account for the metabolic acidosis observed. In addition, 9 of these 11 patients had average infusion rates of less than 550 ml/h, much less than the 3,000 ml/h 0.9% sodium chloride over 2 h required to produce a BE of -6.7 in adult gynecologic surgery patients.²⁰

Discussion

This study provides the first quantitative estimate of the incidence of mild metabolic acidosis during pro-

Table 2. Characteristics of Propofol Radiofrequency Ablation Cases with Metabolic Acidosis

	Other Potential Causes* of Metabolic Acidosis besides Propofol	Propofol Only Apparent Cause of Metabolic Acidosis
Number of cases	37	13
Age, yr	52.5 ± 9.7	57.9 ± 10.6
Average maximal base excess (most negative)	-5.4 ± 2.4	-4.2 ± 1.7
Propofol total dose, mg/kg	20.4 ± 16.0	21.5 ± 14.4
Time receiving propofol, h	7.0 ± 3.3	6.9 ± 3.0
Average propofol infusion rate, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	47.8 ± 32.0	53.6 ± 26.8
Highest propofol infusion rate, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	63.5 ± 56.7	69.4 ± 39.8

* Cardiac dysfunction other than arrhythmia (valvular disease, evidence of ischemia or infarction, intracardiac shunts, or left ventricular ejection fraction $< 40\%$), diabetes mellitus, renal disease with creatinine > 2.0 , hypoxemia (arterial oxygen saturation or pulse oximeter $\leq 96\%$ at any time during the radiofrequency ablation), hypotension (systolic blood pressure ≤ 90 mmHg for 15 or more consecutive minutes), or anemia with hemoglobin < 10.0 g/dl.

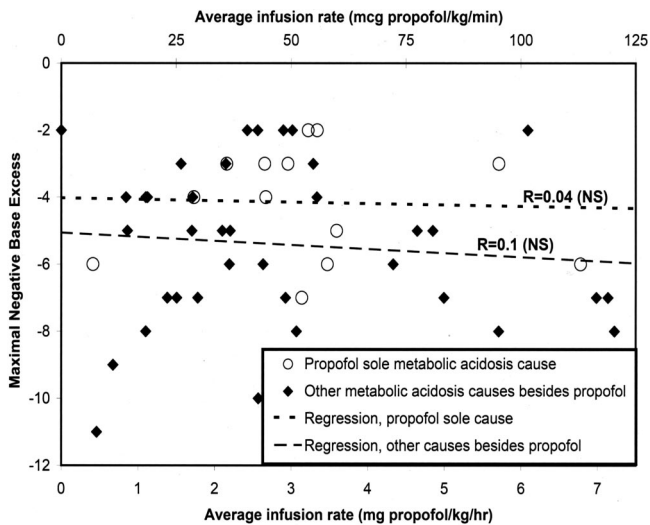


Fig. 1. Relation of maximal negative base excess to average infusion rate of propofol, analyzed separately for patients with and without identifiable cause of metabolic acidosis in addition to propofol. Note that the upper and lower x-axes give alternate measures of propofol dose, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. NS = not significant ($P > 0.05$); R = Pearson product-moment correlation coefficient. Similar analyses also showed no correlation using other measures of propofol dose: total dose (mg/kg), time receiving propofol (hours), and highest infusion rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

longed propofol infusion in non-critically ill patients, where there is no apparent cause of the acidosis except propofol: 24%, significantly greater than the 8% incidence of metabolic acidosis in the nonpropofol comparator group. This surprisingly high incidence is not an indication of the number of patients at risk for serious injury from the fulminant form of propofol infusion syndrome, because the study criterion ($\text{BE} \leq -2$) was designed to detect early, mild, reversible cases. Indeed, none of the patients in this study showed evidence of permanent injury from their mild metabolic acidosis. However, our data do support the hypothesis that clinically significant propofol infusion syndrome is an extreme manifestation of a more common, initially reversible syndrome, rather than an extremely rare, idiosyncratic drug reaction.

The criteria we used for alternate causes of metabolic acidosis were designed to exclude stringently any possible nonpropofol cause. The few cases in the lower left quadrant of figure 1 (low propofol dose, severe metabolic acidosis) are most likely to be those not caused by propofol, although we cannot exclude an effect of propofol to worsen an already significant metabolic acidosis. It is possible that some of the milder alternate cause cases developed a metabolic acidosis secondary to propofol as well (e.g., well-controlled diabetes, mild stable lung disease causing an oxygen saturation measured by pulse oximetry of 94%), so that the incidence of 24% would be an underestimate of the effect of propofol to cause metabolic acidosis.

There are several limitations inherent in the retrospec-

tive nature of this study. However, the study design is unlikely to artifactually increase the observed incidence. Because most ABGs in the propofol RFA patients were drawn as a check on respiratory depression, rather than consistently during the propofol infusion, some cases of metabolic acidosis could have been completely missed. The retrospective study design thus creates a bias toward underestimate, rather than overestimate, of the incidence of mild propofol infusion syndrome.

A secondary objective of this investigation was to determine the dose-response curve of metabolic acidosis related to propofol. However, the data did not display a statistically significant relation between propofol dose and metabolic acidosis (fig. 1). Although this does not add further support to a causal relation, the limitation inherent in a retrospective chart review, with nonuniform, sporadic sampling of ABGs, is the most likely explanation. Most patients had only one or two ABGs sampled, at times that were not necessarily optimized to detect the maximal negative BE. It is also possible that the dose-response relation was obscured because, although the dose was high for sedation (approximately $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), it was relatively low compared with most reported cases of propofol infusion syndrome, with infusions often $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or higher.

Another limitation of this study is that our population of patients undergoing RFA during the study period included almost no patients not receiving propofol, so that there was not a control group identical except for propofol administration. We added CEA patients as a nonpropofol comparator group after the original data analysis of the RFA propofol patients. This provided a comparator group that should compensate for any institution-specific bias in ABG collection method or analysis. Use of CEA patients before surgical incision also provided comparators with low levels of surgical stress similar to the nonsurgical RFA procedure, and an adequate number for statistical comparisons. This did result in a difference in ABG collection time between the groups, with propofol ABGs drawn throughout the anesthetic, and nonpropofol CEA ABGs drawn at the beginning of the anesthetic. However, available data do not suggest a time-dependent change in BE during anesthesia in the absence of factors known to cause metabolic acidosis.²⁰ Our analysis is clearly limited by the lack of a true control group, and must be assessed with caution. However, we could not find any area at our institution that would yield a true control group for a retrospective study such as this, and it is unlikely that we could propose and conduct a prospective study without the estimate of propofol-associated metabolic acidosis provided by this retrospective study.

This study was also limited by not having available other data that would be helpful in determining the etiology of the metabolic acidosis, particularly serum lactate and chloride. Our analysis of potential nonpropo-

fol causes of metabolic acidosis, and of the relation of intravenous saline administration to acidosis, partially compensates for the lack of data on lactate and chloride. A subsequent prospective study should certainly collect this data as well as ABGs. While some reports of propofol infusion syndrome have described elevated serum lactate, until the etiology of the syndrome is better understood, elevated lactate should be considered suggestive rather than a requirement for the diagnosis of the syndrome.

In summary, this study provides evidence that even in a non-critically ill population, prolonged high-dose propofol infusion is associated with otherwise unexplained metabolic acidosis in a significant number of patients, rather than being extremely rare. The study is limited by its retrospective nature and lack of a true control group. A prospective study designed specifically to assess metabolic acidosis during prolonged propofol infusion is needed, but has been difficult to plan in terms of sample size without the data provided here. All of the patients we studied showed no lasting adverse effect from their metabolic acidosis, suggesting that it was reversible. Although this is reassuring, it also suggests that the potential for propofol infusion syndrome exists in a significant part of the population and that caution with frequent surveillance for metabolic acidosis is appropriate with propofol infusions in patients where metabolic acidosis could worsen other disease processes.

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