ORIGINAL CLINICAL REPORT

OPEN

U-Shaped Association Between Carboxyhemoglobin and Mortality in Patients With Acute Respiratory Distress Syndrome on Venovenous Extracorporeal Membrane Oxygenation

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BACKGROUND: Carbon monoxide (CO) is an endogenous signaling molecule that activates cytoprotective programs implicated in the resolution of acute respiratory distress syndrome (ARDS) and survival of critical illness. Because CO levels can be measured in blood as carboxyhemoglobin, we hypothesized that carboxyhemoglobin percent (COHb%) may associate with mortality.

OBJECTIVES: To examine the relationship between COHb% and outcomes in patients with ARDS requiring venovenous extracorporeal membrane oxygenation (ECMO), a condition where elevated COHb% is commonly observed.

DESIGN: Retrospective cohort study.

SETTING: Academic medical center ICU.

PATIENTS: Patients were included that had ARDS on venovenous ECMO.

MEASUREMENTS AND MAIN RESULTS: We examined the association between COHb% and mortality using a Cox proportional hazards model. Secondary outcomes including ECMO duration, ventilator weaning, and hospital and ICU length of stay were examined using both subdistribution and causal-specific hazard models for competing risks. We identified 109 consecutive patients for analysis. Mortality significantly decreased per 1 U increase in COHb% below 3.25% (hazard ratio [HR], 0.35; 95% CI, 0.15–0.80; $p = 0.013$) and increased per 1 U increase above 3.25% (HR, 4.7; 95% CI, 1.5–14.7; $p = 0.007$) reflecting a nonlinear association ($p = 0.006$). Each unit increase in COHb% was associated with reduced likelihood of liberation from ECMO and mechanical ventilation, and increased time to hospital and ICU discharge (all $p < 0.05$). COHb% was significantly associated with hemolysis but not with initiation of hemodialysis or blood transfusions.

CONCLUSIONS: In patients with ARDS on venovenous ECMO, COHb% is a novel biomarker for mortality exhibiting a U-shaped pattern. Our findings suggest that too little CO (perhaps due to impaired host signaling) or excess CO (perhaps due to hemolysis) is associated with higher mortality. Patients with low COHb% may exhibit the most benefit from future therapies targeting anti-oxidant and anti-inflammatory pathways such as low-dose inhaled CO gas.

KEY WORDS: carbon monoxide; carboxyhemoglobin; extracorporeal membrane oxygenation; hemolysis; respiratory distress syndrome

DOI: 10.1097/CCE.0000000000000957

While carbon monoxide (CO) is a well-recognized toxin, substantial evidence accumulated over the last 20 years has also solidified its role in host protection and cell signaling (1–4). CO is

KEY POINTS

Question: The purpose of this study was to examine the relationship between peripheral blood carboxyhemoglobin percent (COHb%) and outcomes in patients with severe acute respiratory distress syndrome (ARDS) requiring venovenous extracorporeal membrane oxygenation (ECMO).

Findings: We performed a retrospective cohort study of 109 consecutive patients and found COHb% associated with mortality in a U-shaped pattern: Mortality significantly decreased per 1 U increase in COHb% below 3.25% and increased per 1 U increase in COHb% above 3.25%.

Meaning: COHb% is a novel biomarker for mortality in patients with ARDS on venovenous ECMO.

produced endogenously by heme oxygenase-1 (HO-1) in response to inflammatory and oxidant insults or hemolysis (5, 6). The CO/HO-1 system activates mitochondrial biogenesis, a program critical for resolution of sepsis and acute respiratory distress syndrome (ARDS) (7–11). HO-1/CO is also bidirectional, as HO-1 and mitochondrial biogenesis can be activated by administering exogenous low-dose inhaled CO gas as a therapy (7–11). Multiple preclinical studies and one phase 1 clinical trial have shown low-dose inhaled CO is safe and may accelerate resolution of inflammation and acute lung injury (1–3, 11–16).

Regardless of whether CO is produced endogenously or delivered via inhalation, CO redistributes in the peripheral blood compartment and can be measured as carboxyhemoglobin percent (COHb%). COHb% has been observed to increase in patients under inflammatory stress, such as patients with ARDS treated with venovenous extracorporeal membrane oxygenation (ECMO) (5, 6, 17); however, it is not clear if this is driven by an adaptive host response, such as the HO-1/CO system, or hemolysis (heme degradation), or both. In an effort to guide future CO-based research, we sought to model the relationship between rising endogenous COHb% and clinical outcomes in patients with ARDS on venovenous ECMO. Because CO is known to activate mitochondrial biogenesis, a cytoprotective program associated with survival of critical illness (18, 19), we hypothesized that whole blood COHb% may be a novel prognostic biomarker for survival. However, CO is also a marker of hemolysis, which can trigger ill effects such as acute kidney injury (20). Therefore, our hypothesis was open-ended as to whether higher COHb% associates with a higher or lower mortality.

METHODS

Study Design

This is a single-center retrospective cohort study including patients with ARDS treated with venovenous ECMO between January 1, 2009, and January 1, 2017, in the Duke University Hospital Medical ICU. Patients were excluded from the study if they were under 18 years old, pregnant at the time of venovenous ECMO cannulation, undergoing venovenous ECMO for an indication other than ARDS, required more than one venovenous ECMO course during the index hospitalization, or if venovenous ECMO had been initiated at an outside hospital more than 48 hours prior to transfer to Duke University Hospital. Data were obtained by chart abstraction and stored in a Research Electronic Data Capture database. The study was approved by the Duke University Institutional Review Board (IRB) on December 22, 2017 (IRB No. Pro00090196, "VV ECMO for Acute Respiratory Failure"). All research activities were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Statistical Analysis

Descriptive statistics regarding demographic and patient characteristics such as clinical and biomarker characteristics are presented using the mean (SD) or median (25–75th percentiles [Q1–Q3]) for continuous variables, and frequency count (percentage) of nonmissing values for categorical variables. The number of missing values for each variable is reported.

We examined the association between the COHb% and the primary and secondary clinical outcomes including survival from date of cannulation, ventilator-free days in first 90 days, ECMO and ventilator duration, hospital and ICU length of stay, and units of blood per venovenous ECMO patient-day. Specifically, we analyzed the average of the COHb% daily peak (the average of the highest COHb% value recorded for each day on venovenous ECMO).

In all models, we adjusted for the Sequential Organ Failure Assessment (SOFA) and Respiratory ECMO Survival Prediction (RESP) scores calculated immediately prior to time of ECMO cannulation. If SOFA or RESP score was missing, the median value was used to avoid excluding patients (n = 2 and 9, respectively). Assumptions of linearity were verified using regression splines and proportional hazards (PHs) assumptions were assessed using Schoenfeld residuals.

For our primary outcome, a Cox PH model was used to evaluate mortality with results presented as the hazard ratio (HR) with 95% CI. Mortality was found to have a significant nonlinear relationship with COHb% and two linear splines were used. Kaplan-Meier survival estimates at day 28 and day 90 are presented with 95% CI.

Secondary outcomes including ECMO duration, ventilator duration, and ICU and hospital length of stay were analyzed using a Cox PH model with death considered as a competing risk using both subdistribution hazards (Fine & Gray's method) and causal-specific hazards (censored at death). Results are presented as the HR with 95% CI. Patients requiring ventilatory support at discharge were censored in models evaluating ventilation weaning. Ventilator-free days assumed a zero-inflated negative binomial model.

An exploratory analysis was done to evaluate the association of hemolysis (defined as "present" or "not present") and dialysis with average daily peak COHb% using the Wilcoxon rank-sum test. Hemolysis was deemed present if one of the following conditions was met: 1) haptoglobin was below the lower limit of normal with one additional hemolysis marker (elevated lactate dehydrogenase, elevated total bilirubin, or decreased fibrinogen) present; 2) two out of three hemolysis markers were present; or 3) there was documented clinical suspicion for hemolysis with one hemolysis marker present. Also, the association of COHb% and units of blood per patient-day on ECMO was analyzed using a regression model with Poisson distribution with results presented as the incidence rate ratio with 95% CI.

All statistical analyses were done using SAS Version 9.4 (SAS Institute, Cary, NC) with statistical significance assessed at level $\alpha = 0.05$.

RESULTS

We identified 109 consecutive patients for analysis. Baseline demographics and clinical characteristics at time of ECMO initiation are shown in **Table 1**. COHb% was measured and averaged over the duration of venovenous ECMO support: The average (SD) of the COHb% daily means was 2.70% (0.89%); the average (SD) of the COHb% daily peaks was 3.26% (0.90%); and average (SD) COHb% peak of the daily peaks was 4.36% (1.42%) (**Table 2**). Additional laboratory values averaged over the duration of venovenous ECMO support are shown in Table 2.

Clinical outcomes of the cohort are shown in **Table 3**. Overall, 74 patients (67.9%) were successfully liberated from venovenous ECMO before death. Of those successfully liberated, the median (Q1–Q3) time to decannulation was 10.5 days (6, 14). Sixty-three patients (57.8%) were successfully weaned from the ventilator after a median (Q1–Q3) of 24 days (14–31 d). Median (Q1–Q3) ventilator-free days at 90 days were 52 days (0–68 d). Overall mortality at 28 and 90 days was 31.4% (95% CI, 23.3–41.6%) and 46.5% (95% CI, 35.7–58.7%), respectively, based on Kaplan-Meier estimates.

We examined mortality using the average daily peak COHb% as a predictor. After adjusting for baseline SOFA and RESP scores, we found a significant decrease in mortality per 1 U increase in COHb% for carboxyhemoglobin below 3.25% (p = 0.013) and a significant increase in mortality per 1 U increase in COHb% for COHb% greater than 3.25% (p = 0.007) (**Table 4**). The association between COHb% and mortality was found to be significantly nonlinear (p = 0.006) (**Fig. 1**).

We examined the secondary clinical outcomes using both subdistribution and causal-specific HRs to consider the association with each outcome conditional on being alive (cause-specific), as well as considering patients who die still at risk for the outcome (subdistribution). Directional trends in longer times until ECMO liberation, ventilator weaning, and hospital and ICU discharge were observed per unit increase in COHb% (all $p < 0.05$) for both model types (Table 4).

In our exploratory analysis using a Poisson regression model, COHb% was not statistically significantly associated with total blood units transfused per venovenous ECMO day (incidence rate ratio, 1.05; 95% CI, 0.88–1.27; p = 0.58), nor was there a significant

TABLE 1.
Baseline Demographics and Clinical Characteristics

Baseline Characteristic	Patient Cohort (n = 109)	Missing
Age (yr)	44.2 (29.7–54.6)	
Sex		
Male	61 (56%)	
Female	48 (44%)	
Race		2 (1.8%)
White	72 (67.3%)	
Black or African American	29 (27.1%)	
Asian	2 (1.9%)	
Native American or Alaska Native	4 (3.7%)	
Ethnicity		
Non-Hispanic/Latino	104 (95.4%)	
Hispanic/Latino	5 (4.6%)	
Body mass index	31.4 (25.9–38.9)	1 (0.9%)
Immunocompromised		1 (0.9%)
No	90 (83.3%)	
Yes	18 (16.7%)	
Acute respiratory distress syndrome etiology		
Viral pneumonia	49 (45%)	
Aspiration pneumonia	18 (17%)	
Nonpulmonary sepsis	13 (12%)	
Pneumonia of unknown etiology	12 (11%)	
Bacterial pneumonia	9 (8%)	
Fungal pneumonia	3 (3%)	
Pancreatitis	2 (2%)	
Unknown	2 (2%)	
Trauma	1 (1%)	
Sequential Organ Failure Assessment score	10 (8–13)	2 (1.8%)
Respiratory ECMO Survival Prediction score	3 (1–6)	11 (10.1%)
pH	7.2 (7.1–7.30)	7 (6.4%)
Pao_2	62 (52–70)	2 (1.8%)
$Paco_2$	55.5 (47–71)	7 (6.4%)
Pao_2/Fio_2 ratio	66 (52–81.3)	2 (1.8%)
Ventilator days prior to venovenous ECMO	2 (0–5)	

ECMO = extracorporeal membrane oxygenation.
Data presented as median (Q1–Q3) or count (%).

association between the average daily peak COHb% and the use of acute dialysis (p = 0.093) (**Table 5**). However, patients with hemolysis had a larger median (Q1–Q3) COHb% compared with patients without hemolysis (3.7 [2.7–4.4] vs 3.1 [2.6–3.7]; p = 0.031; Table 5).

DISCUSSION

In this study, we found that COHb% was associated with mortality in a U-shaped fashion, with the lowest mortality at a COHb% of 3.25% and increasing in either direction away from this value. However, increased COHb% was linearly associated with increased time to ECMO liberation, ventilation liberation, and ICU and hospital time to discharge. Furthermore, elevated carboxyhemoglobin levels were significantly associated with presence of hemolysis, but not with acute kidney injury or blood transfusions.

CO is a biological gas that competes with oxygen to bind hemoglobin and cytochrome c oxidase of the electron transport chain, reducing oxygen carrying capacity and producing cellular hypoxia. Despite these well-known toxic effects, accumulating evidence has also shown CO is generated endogenously by HO-1 in response to oxidant and inflammatory stresses, activating key pro-survival cellular pathways such as mitochondrial biogenesis (1, 12–14, 21–26). As a result, CO has been investigated as a therapy in preclinical studies and human clinical trials in pro-inflammatory disease states such as ARDS and has been shown to reduce mitochondrial DNA damage and mitigate acute lung injury (1–3, 11–16). Because CO levels can be measured clinically using peripheral blood carboxyhemoglobin, we hypothesized that COHb% may be a novel marker of mortality or survival in patients with ARDS on venovenous ECMO. In fact, studies have found elevated blood COHb% (1–2% range) in medically critically ill patients in general (27) and in a variety of inflammatory lung conditions, including chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia, compared with controls (carboxyhemoglobin < 1%) (28, 29). Our study demonstrates that among patients with ARDS on venovenous ECMO, average daily peak COHb% is significantly associated with mortality in a nonlinear fashion, increasing bidirectionally from a COHb% of 3.25%. In contrast to our

TABLE 2.
Laboratory Values During Venovenous Extracorporeal Membrane Oxygenation Course

Laboratory Values	Average of Daily Means	Average of Daily Peaks	Peak of Daily Peaks	Missing
Carboxyhemoglobin (%)	2.70 (0.89)	3.26 (0.90)	4.36 (1.42)	1 (0.9%)
Hemoglobin (g/dL)	9.32 (1.03)			
Lactate dehydrogenase (U/L)	534.90 (235.32)			85 (78.0%)
Haptoglobin (mg/dL)	132.42 (132.06)			96 (88.1%)
Total bilirubin (mg/dL)	1.80 (2.20)			8 (7.3%)
Unconjugated bilirubin (mg/dL)	0.91 (0.92)			32 (29.4%)
Fibrinogen (mg/dL)	418.24 (178.06)			9 (8.3%)
Partial thromboplastin time (s)	53.50 (17.31)			2 (1.8%)
Creatinine (mg/dL)	2.03 (1.59)	2.16 (1.69)	3.27 (2.66)	13 (11.9%)

Data are presented as mean (SD) or count (%).

findings, Bemtgen et al (5) reported a lower mortality in patients on ECMO with a COHb% less than 2% and higher mortality for COHb% greater than 2%. We suspect these discrepant results may be explained by differences in statistical analysis, for instance dichotomizing COHb% above or below 2%, rather than assessing the variable as a continuous measure. For instance, using multivariable logistic regression, Fazekas et al (27) found lower COHb% was associated with higher mortality in medically critically ill patients. Additionally, consistent with our findings, Melley et al (30) also found a U-shaped relationship between COHb% and mortality in patients after cardiac surgery using a multivariable logistic regression model. We performed an unbiased Cox PH model that found a statistically significant nonlinear U-shaped relationship between COHb% and mortality. This relationship is consistent with the known competing effects of CO, and we propose a model wherein patients with low COHb% have impaired activation of the HO-1/CO system, do not attain the beneficial cytoprotective and anti-inflammatory effects of CO, and experience an increased mortality (**eFig.**, http://links.lww.com/CCX/B233). Conversely, patients with high COHb% have a higher incidence of hemolysis and (presumably) cellular hypoxia, or an exaggerated inflammatory response, and we hypothesize one or more of these factors may contribute to their higher mortality. However, because venovenous ECMO is known to cause hemolysis via mechanical and shear forces (31–34), and because hemolysis is significantly associated with increased COHb% (5, 6), we cannot exclude that patients requiring venovenous ECMO for a longer duration will simply accumulate higher COHb%.

While the relationship between COHb% and mortality was nonlinear, the association between COHb% and all secondary outcomes was linear. One explanation for this is while increasing COHb% was associated with prolonged time to clinical improvement, patients within a certain mid-level COHb% range were still more likely to survive their illness, regardless of time to recovery. A prior study also reported an association between increased COHb% and ECMO duration, where every increase in COHb% of 0.0054% ($p < 0.001$) was associated with an additional hour on ECMO dependence (17). Our study advances this finding by showing that COHb% is not only a biomarker for reduced ECMO liberation, it is also associated with reduced ventilator liberation and prolonged ICU and hospital stays. However, we are not able to determine whether this finding is associational or reflects an underlying driver of worsened outcomes.

Patients undergoing regular hemodialysis are known to exhibit an increased COHb% (35, 36). While we did not find a statistically significant association between COHb% and the need for dialysis, it is possible this observation was underpowered, as only 34 patients in the cohort received dialysis. However, there may be differences between acute versus chronic renal replacement therapy, or the type of renal replacement therapy provided. Similarly, banked blood for transfusion may

TABLE 3.
Clinical Outcomes

Clinical Outcome	*n* = 109
VV ECMO liberation	
Time to decannulation or death (d)	10 (5–16)
Liberated from VV ECMO before death	74 (67.9%)
If liberated, VV ECMO duration (d)	10.5 (6–14)
Ventilator weaning	
Time to weaning or death (d)	23 (12–31)
Weaned from ventilator before death	63 (57.8%)
If weaned, ventilator duration (d)	24 (14–31)
Ventilator-free days at 90 d (d)	52 (0–68)
ICU discharge	
Time to ICU discharge or death (d)	22 (11–31)
Discharged from ICU before death	69 (63.3%)
If discharged, ICU length of stay (d)	26 (15–34)
Hospital discharge	
Time to hospital discharge or death (d)	28 (14–41)
Discharged from hospital before death	68 (62.4%)
If discharged, hospital length of stay (d)	35.5 (24.5–51.0)
Blood transfusion	
Received blood transfusion	98 (89.9%)
If transfused, number of units transfused per patient	7 (3–12)
If transfused, number of units per VV ECMO-day	0.58 (0.36–1.00)
Dialysis during VV ECMO	35 (32.1%)
Mortality at 28 d[a]	32 (31.4%)
Mortality at 90 d[a]	41 (46.5%)

VV ECMO = venovenous extracorporeal membrane oxygenation.
[a]Mortality percentage calculated using product-limit survival estimates from Kaplan-Meier curve to allow censoring at hospital discharge.
Data presented as median (Q1–Q3) or count (%).

also contain elevated COHb%, through either donor characteristics or hemolysis (37–39). However, we did not find a statistically significant association between blood transfusions and COHb%. This could reflect the observed trend of reduced COHb% levels in banked blood over time (37), restrictive transfusion practices at our institution, or other unknown factors.

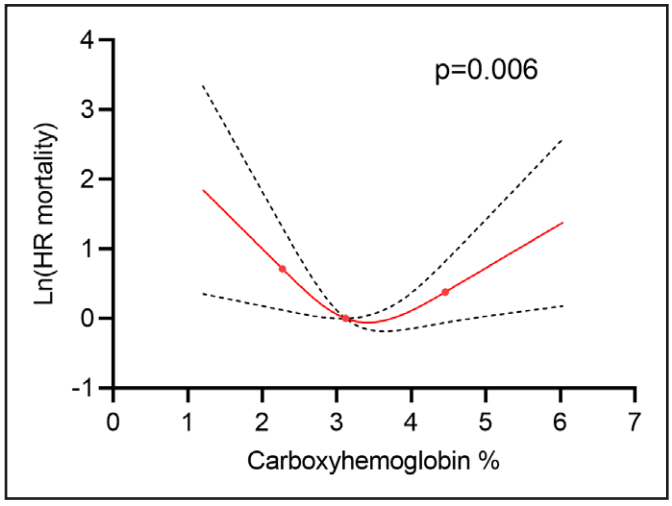

Figure 1. Mortality as a function of carboxyhemoglobin percent (COHb%) in acute respiratory distress syndrome patients on venovenous extracorporeal membrane oxygenation. Carboxyhemoglobin percent is shown on the abscissa and the log-transformed hazard ratio (HR) for mortality is shown on the ordinate. The estimate (*solid red line*) and the 95% CIs (*dotted gray lines*) are shown. The *three knots* are shown as *solid red circles*. The *p* value indicates the association between COHb% and mortality is significantly nonlinear.

Our study is limited by several factors. First, our study was performed at a single center and has not been externally validated. Second, given the inherent limitations of retrospective studies, we cannot ascribe causality and can only hypothesize as to the mechanism of our findings. Third, it is possible there were unmeasured confounders, such as severity of illness, in our cohort that could (partially) account for differences in venovenous ECMO duration, despite our efforts to control this by adjusting for RESP and SOFA scores. We also did not collect data on prevalence of cirrhosis or chronic tobacco use, both of which are known causes of chronic carboxyhemoglobin elevation; however, we suspect very few (if any) patients had cirrhosis as this is generally considered a contraindication to ECMO, and any carboxyhemoglobin elevation due to smoking would have been washed out prior to ECMO deployment due to preceding administration of supplemental oxygen. Fourth, laboratory markers of hemolysis are imperfect and our definition may be inaccurate, which could have affected our exploratory analysis.

In conclusion, our study suggests that there is a mid-range optimal zone within which carboxyhemoglobin levels are associated with the most protection and the lowest mortality. Patients below this zone display

TABLE 4.
Primary and Secondary Outcomes Using Cox Proportional Hazards Models Considering Death As a Competing Risk[a]

Primary Outcome Model	HR (95% CI) (per Unit COHb% Change)			p
Mortality				
COHb% ≤ 3.25	0.349 (0.152–0.799)			0.013
COHb% > 3.25	4.732 (1.524–14.693)			0.007
Secondary Outcome Models	Subdistribution[b] HR (95% CI) (per Unit COHb% Change)	p	Causal-Specific[c] HR (95% CI) (per Unit COHb% Change)	p
Extracorporeal membrane oxygenation liberation	0.706 (0.539–0.924)	0.011	0.428 (0.311–0.589)	< 0.001
Ventilation weaning	0.660 (0.470–0.928)	0.017	0.395 (0.273–0.573)	< 0.001
Hospital discharge	0.666 (0.472–0.938)	0.020	0.470 (0.320–0.689)	< 0.001
ICU discharge	0.656 (0.474–0.908)	0.011	0.420 (0.295–0.596)	< 0.001

COHb% = carboxyhemoglobin percent, HR = hazard ratio.
[a]One patient missing COHb% average daily peak (total *n* = 108).
[b]Fine & Gray's competing risk model.
[c]Censor at death.

TABLE 5.
Association of Carboxyhemoglobin Percent and Exploratory Outcomes

Variable Present	No	Yes[a]	Total	p
Dialysis	74 (67.9%)	34 (32.1%)	108 (100%)	
Average daily peak COHb%	3.1 (2.6–3.7)	3.3 (2.8–4.0)	3.1 (2.6–3.7)	0.093[b]
Hemolysis	82 (75.1%)	26[c] (24.8%)	108 (100%)	
Average daily peak COHb%	3.1 (2.6–3.7)	3.7 (2.7–4.4)	3.1 (2.6–3.7)	0.031[b]

COHb% = carboxyhemoglobin percent.
[a]One patient missing COHb%.
[b]Wilcoxon rank-sum test.
[c]Hemolysis criteria: *n* = 5 patients met criteria 1, *n* = 14 patients met criteria 2, and *n* = 7 patients met criteria 3 (see *Methods* section).
Data presented as median (Q1–Q3) or count (%).

increased mortality and may be prime candidates to study therapies such as low-dose inhaled CO aimed at activating cytoprotective pathways. Patients above this zone also display increase mortality that may be due to hemolysis or hypoxia and may benefit from mitigating these deleterious processes. Furthermore, future studies could further explore the relationship between COHb%, tissue hypoxia, and mortality by measuring cellular respiration.

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Drs. Meservey, Krishnan, Rackley, and Kraft were involved in conception or design of the work. Drs. Green and Morrison were involved in statistical analysis. Drs. Meservey and Kraft were involved in drafting of the article. All authors were involved in acquisition, analysis, or interpretation of data; critically revising the article; and final approval of the article.

Dr. Rackley reports honoraria from Inspira and Roche. Dr. Kraft reports grant funding from the Department of Defense, National Institutes of Health, and Bluejay Diagnostics; and honoraria from Eli Lilly, Bluejay Diagnostics, and GST Micro. The remaining

authors have disclosed that they do not have any potential conflicts of interest.

Drs. Rackley and Kraft shared senior-authorship.

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