

Electrocardiographic ST-segment Changes during Acute, Severe Isovolemic Hemodilution in Humans

Jacqueline M. Leung, M.D., M.P.H., Richard B. Weiskopf, M.D.,† John Feiner, M.D.,‡ Harriet W. Hopf, M.D.,§ Scott Kelley, M.D.,‖ Maurene Viele, M.D.,# Jeremy Lieberman, M.D.,‡ Jessica Watson, M.A.,** Mariam Noorani, B.A.,†† Darwin Pastor,†† Hooi Yeap, R.N.,‡‡ Rachel Ho, B.S.,‡‡ Pearl Toy, M.D.§§*

Background: **Controversy exists regarding the lowest blood hemoglobin concentration that can be safely tolerated. The authors studied healthy resting humans to test the hypothesis that acute isovolemic reduction of blood hemoglobin concentration to 5 g/dl would produce an imbalance in myocardial oxygen supply and demand, resulting in myocardial ischemia.**

Methods: **Fifty-five conscious healthy human volunteers were studied. Isovolemic removal of aliquots of blood reduced blood hemoglobin concentration from 12.8 ± 1.2 to 5.2 ± 0.5 g/dl (mean ± SD). Removed blood was replaced simultaneously with intravenous fluids to maintain constant isovolemia. Hemodynamics and arterial oxygen content (Cao_2) were measured before and after removal of each aliquot of blood. Electrocardiographic (ECG) changes were monitored continuously using a Holter ECG recorder for detection of myocardial ischemia.**

Results: **During hemodilution, transient, reversible ST-segment depression developed in three subjects as seen on the electrocardiogram during hemodilution. These changes occurred at hemoglobin concentrations of 5–7 g/dl while the subjects were asymptomatic. Two of three subjects with ECG changes had significantly higher heart rates than those without ECG changes at the same hemoglobin concentrations. When evaluating the entire study period, the subjects who had ECG ST-segment changes had significantly higher maximum heart rates than those without ECG changes, despite having similar baseline values.**

Conclusion: **With acute reduction of hemoglobin concentration to 5 g/dl, ECG ST-segment changes developed in 3 of 55 healthy conscious adults and were suggestive of, but not conclusive for, myocardial ischemia. The higher heart rates that developed during hemodilution may have contributed to the development of an imbalance between myocardial supply and demand resulting in ECG evidence of myocardial ischemia. However, these ECG changes appear to be benign because they were reversible and not accompanied by symptoms. (Key words: Anemia; ECG; myocardial ischemia.)**

THERE is an abundance of data from experimental animal studies indicating that extreme hemodilution is well-tolerated by the normal heart at rest. However, human data are limited concerning the threshold necessary for blood transfusion. Clinical outcome studies[1,2] and review of the literature[3] suggest a potential association between certain threshold of hemoglobin and adverse cardiac outcomes, but they did not directly establish the mechanisms for such an association. Other authors have suggested that hemoglobin levels have no association with adverse outcomes.[4–6] As a result, controversy continues to exist regarding the lowest blood hemoglobin concentration that can be safely tolerated in the perioperative period.

In conscious, healthy, resting humans, we recently demonstrated that acute isovolemic reduction of blood hemoglobin concentration to 5 g/dl, including a decrease in oxygen delivery as low as 6.1 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ using esmolol administration, does not produce evidence of inadequate systemic oxygen delivery.[7,8] Furthermore, in these previous studies, we found that Holter ECG ST-segment changes occurred in 2 of 18 subjects.[8] Accordingly, we designed a larger study to further investigate the cardiovascular and hemodynamic responses to acute, severe isovolemic hemodilution in healthy volunteers using continuous Holter ECG and hemodynamic monitoring as a continuation of our previous work. Our study aimed to test the hypothesis that severe hemodilution to 5 g/dl would produce an imbalance of myocardial supply and demand, resulting in myocardial ischemia as detected by ECG ST-segment changes in conscious humans at rest.

Methods

After obtaining approval from our institutional review board and informed consent from each study participant, we studied 67 healthy volunteers not undergoing surgery. All volunteers were without cardiovascular, pulmonary, or hepatic disease, did not smoke, and were not taking drugs with cardiovascular actions.

Two peripheral venous cannulae and one radial arterial cannula were inserted in each subject using local anesthesia. After insertion of the cannulae, subjects rested for 30 min before measurement of variables. Pulmonary artery catheters used for other simultaneous studies were inserted in the first 17 subjects who were sedated with intravenous propofol infusion (50–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during catheter placement (all 17 subjects included in the current analysis). These simultaneous

* Associate Professor in Residence, ‡ Assistant Professor, ‖ Associate Clinical Professor, †† Research Associate, Departments of Anesthesia and Perioperative Care, † Professor, Departments of Anesthesia and Perioperative Care, Physiology, and the Cardiovascular Research Institute, § Associate Professor in Residence, Departments of Anesthesia and Perioperative Care and Surgery, # Assistant Professor, ** Senior Statician, ‡‡ Research Associate, §§ Professor, Laboratory Medicine. ‡Current position: Department of Anesthesia, University of Michigan, Ann Arbor, Michigan.

Received from the Departments of Anesthesia and Perioperative Care, Surgery, Laboratory Medicine, and the Cardiovascular Research Institute, University of California, San Francisco. Supported in part by US Department of Defense contract # DAMD17-95-C-5006 (RBW) and the National Heart, Lung and Blood Institute Grant # 1 P50 HL54476 (PT), University of California, San Francisco, California. These studies were carried out in part in the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by the National Center for Research Resources, 5 MO1 RR-00079, U.S. Public Health Service.

Address correspondence to Dr. Leung: University of California, San Francisco, Department of Anesthesia and Perioperative Care, 1600 Divisadero Street, California 94143-1605. Address electronic mail to: jmleung@itsa.ucsf.edu.

studies involved measuring other physiologic functions, such as subcutaneous oxygen pressure[9]; cognitive function[10]; and physical well-being, such as fatigue,[11] none of which interfered with the end points measured in this study. Eight of the study subjects received esmolol infusion after hemodilution for a separate study,[7] but the period beginning with esmolol infusion was excluded from the current analysis. Intraarterial blood pressure and heart rate were measured before removal of any blood, and 5–10 min after isovolemic removal of each 450–900 m blood (into CPDA-1 collection bags; Baxter Healthcare Corp., Deerfield, IL). Removal of each 450 ml of blood took approximately 10 min. Isovolemia was maintained by intravenous infusion of 5% human serum albumin (Baxter Healthcare, Glendale, CA) or the subject's platelet rich plasma (after separation from the erythrocytes of the removed blood). Albumin was used in all study subjects until the subject's plasma became available, generally after the first 2 units of blood had been removed and centrifuged. These were infused simultaneously with blood removal, in quantities approximately 10% greater than that of the removed blood, to maintain isovolemia.[8] Hemodilution continued until a target hemoglobin of approximately 5 g/dl was reached. At the time of cardiovascular measurements, arterial blood was sampled for measurement of pressure of oxygen (Po_2), pressure of carbon dioxide (Pco_2), *p*H, base excess (Model #1640, Instrumentation Laboratory; Lexington, MA); hemoglobin and oxyhemoglobin saturation (OSM3 Hemoximeter; Radiometer, Copenhagen, Denmark). Calculation of arterial oxygen content (Cao_2) was performed using the standard formula. Subject body temperature was maintained at 37°C by body surface warming with heated air (Bair Hugger Model 1200; Augustine Medical Inc., Eden Prarie, MN) and by warming the infused fluids.

Electrocardiography was monitored using a three-channel Holter ECG recorder (Del Mar model 459; Del Mar Avionics, Irvine, CA) in all subjects. The ECG was recorded continuously from 1 h before through the completion of the study. The frequency response of the Holter recorder met the American Heart Association specification for ST changes, the cutoff limit being 0.05 Hz for low frequency and 100 Hz for high frequency. For Holter monitoring, three bipolar leads: CC5, modified CM5, and ML were used.[12] Each ECG recording on Holter tapes was scanned visually using an ECG analysis system (Del Mar Model 750). All normal QRS complexes were identified, and all abnormal QRS complexes (*e.g.,* ventricular ectopic beats and conduction abnormalities) were excluded from ST-segment analysis. Continuous ST-segment trends were generated for the entire tape. All possible ST-segment changes meeting criteria as "ischemic episodes" were reviewed and verified by investigators who were blind to patient identity and hemoglobin concentration. An ischemic episode was defined as a reversible ST-segment shift from baseline of 0.1 mV depression or more at J + 60 ms or 0.2 mV elevation or more at the J point lasting for at least 1 min. The time after the J point chosen to measure ST-segment depression was adjusted to exclude the T wave during tachycardia.

To further evaluate the myocardial supply and demand balance, we evaluated the quotient mean arterial blood pressure–heart rate (MAP–HR)[13] and the minimum Cao_2 level (lowest Cao_2 level achieved at any time during hemodilution) in all study subjects.

Statistical Analyses

The Wilcoxon signed rank test was used to test changes from baseline to nadir hemoglobin. The Mann-Whitney U test (exact calculations) was used to test the difference between continuous variables for subjects with and without ECG changes. A P value of < 0.05 (two-sided) was considered to be statistically significant.

Results

Seventeen subjects reported in previous studies[7,8] are included in the current analysis. Twelve subjects for whom Holter ECG data were unusable were excluded, resulting in a total of 55 subjects eligible for the analysis. The data were unusable because of artifacts resulting from poor skin contact with the ECG electrodes. The mean (± SD) age of the study subjects was 27 ± 5 yr. Twenty-nine subjects were women and 26 were men. The mean weight was 67 ± 11 kg and the mean body surface area was 1.78 ± 0.18 m^2. Blood hemoglobin concentration was reduced from a baseline of 12.8 ± 1.2 g/dl to 5.2 ± 0.5 g/dl (range, 4.6–6.7 g/dl) over a mean study period of 2.79 ± 0.74 h. A mean of 8 ± 2 units of blood was removed.

Hemodynamic Indices of Supply and Demand

With severe anemia (lowest hemoglobin reached), heart rates increased from 63 ± 11 (baseline measured before hemodilution began) to 94 ± 14 beats/min (a mean increase of 51 ± 27%; $P < 0.0001$), whereas mean arterial blood pressure decreased from 87 ± 10 to 76 ± 11 mmHg (a mean decrease of 12 ± 13%; $P < 0.0001$), mean diastolic blood pressure decreased from 67 ± 10 to 56 ± 10 mmHg (a mean decrease of 15 ± 16%; $P < 0.0001$), and mean systolic blood pressure decreased from 131 ± 15 to 121 ± 16 mmHg (a mean decrease of 7 ± 11%; $P = 0.0001$).

Electrocardiographic Changes

In three subjects, transient, reversible ST-segment depression developed, as seen during Holter ECG monitoring. Figure 1 shows the changes in the ECG ST segment in one subject.

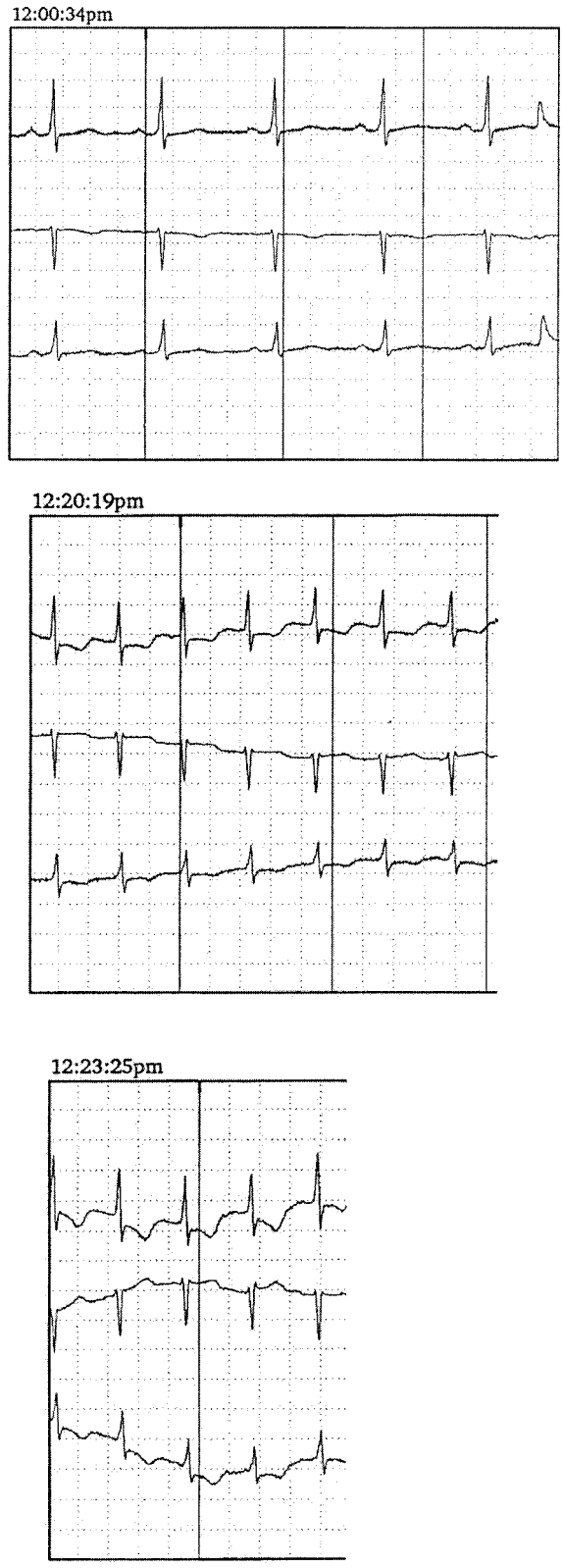

Fig. 1. (*Top*) Hard copy of a three-channel Holter ECG recording obtained immediately before ST-segment depression occurred. (*Middle*) The onset of ECG ST-segment depression. Note new ST-segment depression in channels one and three (*top* and *bottom* ECG tracings). (*Bottom*) ECG recording at maximum ECG ST-segment depression.

Patient 1. The first subject had reversible ST-segment depression that lasted for 12 min during the removal of the fifth and sixth units of blood, at which time, the hemoglobin concentration was 5–6 g/dl. At the onset of ECG ST-segment depression, the subject's heart rate increased from 110 beats/min to a maximum of 140 beats/min during the episode, and returned to 110 beats/min as the ST-depression resolved. Compared with the prehemodilution baseline heart rate (60 beats/min), the maximal heart rate increase during ECG changes represented a 133% increase. Mean arterial blood pressure, however, remained unchanged. Coinciding with the ST-segment changes, this subject had a positional change from supine to sitting in order to urinate. The ST changes resolved as the subject resumed the supine position. Further reduction of the hemoglobin concentration to 4.9 g/dl did not produce ST changes as heart rate decreased to 100 beats/min.

Patient 2. The second subject had reversible ST-segment depression that lasted 46 min during the removal of the sixth unit of blood, at which time the hemoglobin concentration was 6 g/dl. The subject's heart rate increased from 80 beats/min before the onset of ECG changes to a maximum of 110 beats/min during the episode. The ST-changes resolved as heart rate decreased to 94 beats/min with the administration of esmolol as part of a separate protocol in a subset of patients. Compared with the prehemodilution baseline heart rate (72 beats/min), the maximum heart rate reached during an episode of ECG changes represented a 53% increase. Mean arterial blood pressure was reduced by 23% (from a pretransfusion baseline mean arterial blood pressure of 96 to 74 mmHg).

Patient 3. Reversible ST-segment depression developed in the third subject and lasted for 10 min. This episode occurred after removal of the eighth unit of blood, immediately before the return of the first unit of blood to the subject. During this period, the hemoglobin concentration was 6.7 g/dl and heart rate increased from 85 beats/min before the onset of ECG changes to a maximum of 135 beats/min during the episode. Compared with the prehemodilution baseline heart rate of 58 beats/min, the maximum heart rate increase during the episode of ECG changes represented an increase of 133%. Mean arterial blood pressure was reduced 8% (from a prehemodilution baseline of 84 mmHg to 77 mmHg).

For all three subjects, ST-segment depression returned to baseline as heart rates decreased (fig. 2). Symptoms of chest pain, shortness of breath, or dysrhythmia were not detected during real-time ECG monitoring during the period of ECG changes.

Comparison between Subjects with and without Electrocardiographic Changes

We evaluated whether the heart rate increases from baseline during the episode of ECG changes were signif-

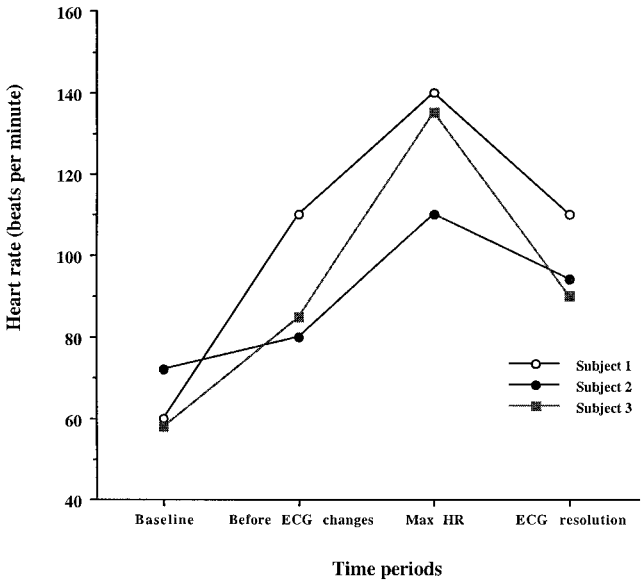

Fig. 2. Changes in heart rate at different time periods for the three subjects with ECG ST-segment depression. Baseline = baseline measurement before hemodilution, before ECG changes = immediate before ST-segment deviation occurs, max HR = maximum heart rate reached during episode of ECG ST-segment changes, ECG resolution = at the offset of ECG changes. See text for additional details.

icantly higher for subjects with ECG changes compared with those without ECG changes at similar hemoglobin concentrations. The increases in heart rate during episodes of ECG changes were significantly greater for two subjects with such changes at hemoglobin levels of 6 and 7 g/dl compared with subjects without ECG changes at the same hemoglobin concentrations (table 1).

When evaluating the entire study period (reduction of hemoglobin from 12.8 ± 1.2 g/dl to 5.2 ± 0.5 g/dl), the subjects who showed ECG ST-segment changes overall had significantly higher maximum heart rates than those without such changes, despite having similar baseline values (table 2). However, the two groups were not significantly different with regard to the maximal percent change from baseline (table 3).

In evaluating myocardial oxygen supply, the subjects with ECG changes had similar minimum Cao_2 than those without, 7.4 ± 0.7 versus 7.7 ± 0.7 ml/100 ml ($P = 0.24$). The minimum value during episodes of ST-segment depression for the subjects with such changes *versus* the minimum value at any time for the other subjects were also similar: 7.9 ± 1.6 and 7.7 ± 0.7 (95% confidence intervals of 3.9 to 11.8 and 7.5 to 7.9, $P = 0.53$). The lowest hemoglobin concentrations achieved in the subjects with and without ECG changes were not significantly different (5.0 ± 0.46 *vs.* 5.3 ± 0.47 g/dl; $P > 0.05$).

Discussion

Reversible ECG ST-segment depression was seen in three (5%) of the study subjects by Holter monitoring, at hemoglobin concentrations of 5–7 g/dl. The subjects with ECG changes overall had higher heart rates during the episodes of ST-segment changes than did the other volunteers at similar hemoglobin concentrations. The marked tachycardia observed during the periods with ECG changes may have contributed to the development of an imbalance between myocardial supply and demand.

Previous experimental studies showed that extreme hemodilution was well-tolerated by the normal heart with a stable work requirement.[14–17] However, after reaching maximal coronary arterial vasodilation, which occurs at a hemoglobin level of 5 g/dl,[16,18] relatively modest additional hemodilution may compromise myocardial oxygenation and contractile function.[14,15,19] Furthermore, redistribution of coronary blood flow and subendocardial ischemia occur when hemoglobin is reduced to less than 5 g/dl.[20] Less severe levels of anemia (5–10 g/dl) are also associated with subendocardial ischemia when oxygen requirements are raised simultaneously.[18]

At a hemoglobin concentration of 5 g/dl in healthy resting humans, cardiac index increases (87%) as a result

Table 1. Comparison of Increases in Heart Rates at Comparable Hemoglobin Concentrations for Subjects with and without ECG Changes

Variable	Presence of ECG Changes	Mean ± SD	Median	*P* Value*
% HR change from baseline to hemoglobin 5	No (n = 37)	57 ± 24	58	0.79
	Yes (n = 1)	53	53	
% HR change from baseline to hemoglobin 6	No (n = 41)	46 ± 20	43	0.048†
	Yes (n = 1)	133	133	
% HR change from baseline to hemoglobin 7	No (n = 42)	44 ± 19	39	0.0465†
	Yes (n = 1)	133	133	

The mean (± SD) percentage increases in heart rates compared with prehemodilution baseline at hemoglobin concentrations 5, 6, and 7 mg/dl are presented for subjects with (at time of ST-segment depression) and without ECG changes. Although the hemoglobin concentration was always measured at the nadir, not all study subjects had their hemoglobin concentrations measured at every hemoglobin concentration. As a result, the comparisons provided in this table indicated those subjects who had hemoglobin concentrations measured exactly at either 5, 6, or 7 g/dl.

* *P* values from the Mann-Whitney test using exact calculations.

† Indicates significant difference between the patients with and without ECG changes.

ECG = electrocardiographic; HR = heart rate.

Table 2. Comparison of Hemodynamic Data and CaO_2 between Subjects with and without ECG Changes

Variable	Presence of ECG changes	Mean ± SD	*P* Value*
Baseline HR (beats/min)	No (n = 52)	64 ± 11	0.97
	Yes (n = 3)	63 ± 8	
Baseline MAP (mmHg)	No (n = 52)	87 ± 11	0.33
	Yes (n = 3)	92 ± 7	
Baseline MAP/HR (mmHg/beats/min)	No (n = 52)	1.42 ± 0.32	0.42
	Yes (n = 3)	1.46 ± 0.13	
Baseline Cao_2 (ml/100 ml)	No (n = 42)	17.8 ± 1.5	0.28
	Yes (n = 3)	16.8 ± 0.7	
Maximum HR (beats/min)	No (n = 52)	97 ± 11	0.005†
	Yes (n = 3)	121 ± 17	
Minimum MAP (mmHg)	No (n = 52)	70 ± 11	0.79
	Yes (n = 3)	72 ± 6	
Minimum MAP/HR (mmHg/beats/min)	No (n = 52)	0.76 ± 0.12	0.34
	Yes (n = 3)	0.70 ± 0.10	
Minimum Cao_2 (ml/100 ml)	No (n = 42)	7.7 ± 0.7	0.24
	Yes (n = 3)	7.4 ± 0.7	

The baseline variables were measured before hemodilution began. The maximum and minimum values were measured at any time during the study period.

* *P* values from the Mann-Whitney test using exact calculations.

† Indicates significant difference between the patients with and without ECG changes.

Cao_2 = arterial oxygen content; ECG = electrocardiographic; HR = heart rate; MAP = mean arterial pressure.

of a substantial increase in heart rate (59%), and to a smaller extent, stroke volume index (19%).[8] The differences in heart rate response between our studies and those in anesthetized humans[21] may be related to the effects of opioids and anesthetics on cardiac filling pressures and heart rate. In unanesthetized dogs, the increase in cardiac output is largely a result of heart rate increase,[22,23] whereas, in dogs anesthetized with barbiturates, the increase is mostly caused by stroke volume[24] and during chlorolose–urethane anesthesia, the increase in cardiac output is a result of both increases in stroke volume and heart rate.[25] The magnitude of these changes is important in determining myocardial oxygen cost. Importantly, oxygen consumption increases more when cardiac output is increased as a result of increased heart rate rather than of increased stroke volume.[26]

Is there evidence in our study subjects that myocardial oxygen supply did not meet the increase demand? One of the subjects who showed ECG changes changed position at a time that coincided with the short episode of ST-segment depression. It is possible that the positional change resulted in ST-segment deviation that is nonischemic in origin. For the other two subjects in whom ECG ST-segment depression developed, the increases in heart rate during the periods of ECG changes were significantly higher than those in subjects without ECG changes at similar hemoglobin concentrations. Two subjects in particular had substantial increases in heart rate (133%) compared with baseline values during the period of ECG ST-depression, despite not being at the nadir of hemodilution (6 to 7 g/dl). These marked increases in heart rate during periods of ST-changes suggest a parallel increase in myocardial oxygen cost while myocardial oxygen supply is at its lowest levels. Given the higher heart rates at similar hemoglobin concentrations, subjects in whom ECG changes developed probably had lower coronary artery blood supply relative to the work performed than the subjects without ECG changes. However, we should emphasize that these ECG changes appear to be benign because they were reversible, and symptoms or signs of myocardial injury did not develop in the subjects.

In the absence of coronary obstruction, ECG changes are probably caused by a discrepancy between myocar

Table 3. Comparison between Groups of Percent Change of Hemodynamic Values from Prehemodilution Baseline to the Maximal Values for Each Subject

Variable	Presence of ECG Changes	Mean ± SD	*P* Value
% Change from baseline to maximum HR	No (n = 52)	56 ± 21	0.11
	Yes (n = 3)	94 ± 45	
% Change from baseline to minimum MAP	No (n = 52)	−19 ± 11	0.44
	Yes (n = 3)	−22 ± 2	
% Change from baseline to minimum MAP/HR	No (n = 52)	−45 ± 9	0.15
	Yes (n = 3)	−52 ± 4	
% Change from baseline to minimum Cao_2	No (n = 42)	−56 ± 5	1.0
	Yes (n = 3)	−56 ± 6	

The baseline variables were measured before hemodilution began. The maximum and minimum values were measured at any time during the study period.

Cao_2 = arterial oxygen content; HR = heart rate; MAP = mean arterial pressure.

dial oxygen requirements and available subendocardial oxygen supply. However, nonischemic causes of ST-segment changes exist. For example, changes in cellular fluxes of electrolytes, ventilation, and drug effects may acutely affect the ST-segment. In women, exercise-induced ST-segment depression is frequent.[27] The predictive value of exercise-induced ST-segment changes in asymptomatic subjects has been evaluated with use of coronary angiography. Although these studies have not been performed in asymptomatic women, ST-segment depression has been shown to have a low predictive value for identification of hemodynamically significant obstructive coronary artery lesions in asymptomatic men.[28]

We cannot determine whether the ECG changes in our subjects represent nonischemic changes. We used ECG ST-segment monitoring in our study as a marker of myocardial ischemia and not to predict the likelihood of the subject having an obstructed coronary artery. Myocardial ischemia can occur in the absence of obstructive coronary artery lesions. In the absence of ventilatory and drug effects, for at least two of the three subjects, the ECG changes may have been ischemic in origin. The use of hard-copy validation of each ECG complexes enable us to eliminate erroneous measurement of ST-segment deviation, especially during periods of tachycardia when the ST-segment acquisition points need adjustment.[29]

Our current and previous results agree with previous studies that discrepancies may occur between metabolic and ECG measurements of ischemia[30] because regional myocardial ischemia may be present during global lactate extraction. Also, systemic measurements of lactate may not be sufficiently sensitive to detect transient ischemia. However, estimation of myocardial lactate extraction from coronary sinus blood samples is not possible in conscious volunteers.

Although the subjects in whom ECG changes developed had higher heart rates at comparable levels of hemoglobin concentrations, we cannot define a critical value for any specific hemodynamic parameter at which ECG ST-segment depression occurs as a result of the small number of subjects with such changes in our study.

Our results are not directly applicable to subjects who are anesthetized. General anesthesia decreases total body and myocardial oxygen consumption, and opioids, which are frequently administered, decrease heart rate. Also, our results may not be applicable to older patients or to those for whom duration of severe hemodilution may be more prolonged. In these situations, higher concentrations of hemoglobin may be necessary. Our recent study in which esmolol infusion was used during hemodilution would suggest that limiting heart rate increases may have potential beneficial effects in reducing myocardial oxygen demand, despite reduction of oxygen delivery.[7]

We did not directly measure total blood volume to assess its adequacy during hemodilution and fluid replacement. However, our methods were identical to our previous studies[7,8] in which cardiac filling pressures were measured by pulmonary artery catheters to maintain isovolemia. Furthermore, the volume of albumin and autologous plasma administered to maintain constant cardiac filling pressures agrees with the degree of intravascular retention of albumin.[31]

In summary, acute isovolemic reduction of hemoglobin concentration to 5 g/dl in conscious, healthy subjects produced ECG ST-segment depression in 3 of 55 conscious volunteers. This may have been a reflection of myocardial ischemia in this small number of individuals. The maximum heart rates during the study period may have contributed to the development of an imbalance between myocardial supply and demand. If we assume that the development of tachycardia during acute anemia contributed to the development of some of the ECG ST-segment depression, using real-time ECG ST-trend monitoring to detect ECG ST-segment changes in patients with substantial tachycardia during severe levels of anemia may be advisable.

The authors thank Peter Bacchetti, Ph.D., Adjunct Professor, Department of Epidemiology and Biostatistics, University of California, San Francisco, for statistical advice provided by

References

1. Hebert P, Wells G, Blajchman M, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: Transfusion requirements in critical care investigators Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999; 340:409–17

2. Carson J, Duff A, Berlin J, Lawrence V, Poses R, Huber E, O'Hara D, Noveck H, Strom B: Perioperative blood transfusion and postoperative mortality. JAMA 1998; 279:199–205

3. Viele M, Weiskopf R: What can we learn about the need for transfusion from patients who refuse blood? The experience with Jehovah's Witnesses. Transfusion 1994; 34:396–401

4. Spahn D, Zollinger A, Schlumpf R, Stohr S, Seifert B, Schmid E, Pasch T: Hemodilution tolerance in elderly patients without known cardiac disease. Anesth Analg 1996; 82:681–6

5. Johnson R, Thurer R, Kruskall M, Sirosis C, Gervino E, Critchlow J, Weintraub R: Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992; 104:307–14

6. Spence R, Carson J, Poses R, McCoy S, Pello M, Alexander J, Popovich J, Norcross E, Camishion R: Elective surgery without transfusion: Influence of preoperative hemoglobin level and blood loss on mortality. Am J Surg 1990; 159:320–4

7. Lieberman J, Weiskopf R, Kelley S, Feiner J, Noorani M, Leung J, Toy P, Viele M: Critical oxygen delivery in conscious humans is less than 7.3 ml O2.kg−1.min−1. ANESTHESIOLOGY 2000; 92:407–13

8. Weiskopf R, Viele M, Feiner J, Kelley S, Lieberman J, Noorani M, Leung J, Murray W, Toy P, Moore M: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998; 279:217–21

9. Hopf H, Viele M, Watson J, Feiner J, Weiskopf R, Hunt T, Noorani M, Yeap H, Ho R, Toy P: Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. Arch Surg; in press

10. Weiskopf R, Kramer J, Viele M, Neumann M, Feiner J, JJ W, Hopf H, Toy P: Acute severe isovolemic anemia impairs cognitive function and memory in humans. ANESTHESIOLOGY (in press)

11. Toy P, Feiner J, Viele M, Watson J, Yeap H, Weiskopf R: Fatigue during acute isovolemic anemia in healthy resting humans. Transfusion 2000; 40:457–60

12. Chaitman B, Hanson J: Comparative sensitivity and specificity of exercise electrocardiographic lead systems. Am J Cardiol 1981; 47:1335–49

13. Buffington C: Hemodynamic determinants of ischemic myocardial dysfunction in the presence of coronary stenosis in dogs. ANESTHESIOLOGY 1985; 63:651–62

14. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N: The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. Basic Res Cardiol 1977; 72:344–64

15. Jan K, Chien S: Effect of hematocrit variations on coronary hemodynamics and oxygen utilization. Am J Physiol 1977; 233:H106–13

16. Von Restorff W, Hofling B, Holtz J, Bassenge E: Effect of increased blood fluidity through hemodilution on coronary circulation at rest and during exercise in dogs. Pflugers Arch 1975; 357:15–24

17. Levy P, Kim S, Eckel P, Chavez R, Ismail E, Gould S, Salem M, Crystal G: Limit to cardiac compensation during acute isovolemic hemodilution: Influence of coronary stenosis. Am J Physiol 1993; 265:H340–9

18. Buckberg G, Brazier J: Coronary blood flow and cardiac function during hemodilution, Intentional hemodilution. Edited by Messmer K, Schmid-Schonbein H. Basel, Karger, 1975, pp 173–89

19. Levine E, Rosen A, Sehgal L, Gould S, Sehgal H, Moss G: Physiologic effects of acute anemia: Implications for a reduced transfusion trigger. Transfusion 1990; 30:11–4

20. Brazier J, Cooper N, Maloney J Jr., Buckberg G: The adequacy of myocardial oxygen delivery in acute normovolemic anemia. Surgery 1974; 75:508–16

21. Fontana J, Welborn L, Mongan P, Sturm P, Martin G, Bunger R: Oxygen consumption and cardiovascular function in children during profound intraoperative normovolemic hemodilution. Anesth Analg 1995; 80:219–25

22. Glick G, Plauth Jr W, Braunwald E: Role of the autonomic nervous system in the circulatory response to acutely induced anemia in unanesthetized dogs. J Clin Invest 1964; 43:2112–24

23. von Restorff W, Hofling B, Holtz J, Bassenge E: Effect of increased blood fluidity through hemodilution on general circulation at rest and during exercise in dogs. Pflugers Arch 1975; 357:25–34

24. Murray J: Venous oxygenation and circulatory responses to oxygen inhalation in acute anemia. Am J Physiol 1964; 207:228–34

25. Escobar E, Jones N, Rapaport E, Murray J: Ventricular performance in acute normovolemic anemia and effects of beta blockade. Am J Physiol 1966; 211:877–84

26. Braunwald E: The determinants of myocardial oxygen consumption. Physiologist 1969; 12:65–93

27. Cumming G, Dufresne C, Samm J: Exercise ECG changes in normal women. CMAJ 1973; 109:108–11

28. Froelicher V, Thompson A, Longo M Jr, Triebwasser J, Lancaster M: Value of exercise testing for screening asymptomatic men for latent coronary artery disease. Prog Cardiovas Dis 1976; 18:265–76

29. Leung J, Voskanian A, Bellows W, Pastor D: Automated electrocardiograph ST-segment trending monitors: Accuracy in detecting myocardial ischemia. Anesth Analg 1998; 87:4–10

30. Haggmark S, Hohner P, Ostman M: Comparison of hemodynamic, electrocardiographic, mechanical and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. ANESTHESIOLOGY 1989; 70:19–25

31. Payen J, Vuillez J, Geoffray B, Lafond J, Comet M, Stieglitz P, Jacquot G: Effects of preoperative intentional hemodilution on the extravasation rate of albumin and fluid. Crit Care Med 1997; 25:243–8