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Ischemia-modified albumin increases after skeletal muscle ischemia during arthroscopic knee surgery

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Abstract

Background: Ischemia can alter the ability of albumin to bind free metal atoms. Based on these biochemical changes, methods to quantify ischemia modified albumin (IMA) were developed to assist in the evaluation of patients with symptoms of cardiac ischemia. Since ischemia can occur in any vascular bed, the specificity of IMA for cardiac muscle ischemia is unclear and requires further investigation.
Methods: We evaluated the specificity of an IMA test in patients with skeletal muscle ischemia during arthroscopic knee surgery. A pressurized thigh cuff was continuously inflated to 300 mm Hg on the operative leg, in order to arrest blood flow during the procedure. Samples were collected before surgery, 15 min after surgery, and prior to discharge.
Results: Twenty-three patients were enrolled in the study. Median tourniquet time was 29 min (range 19–108). Median pre-operative IMA was 90.2 KU/l (range 77–101.6). Statistically significant ($p<0.05$) increases in IMA and myoglobin concentrations, and decreases in albumin concentrations were observed following tourniquet release and before discharge.
Conclusions: Post-operative myoglobin elevations indicated that skeletal muscle ischemia was sufficient to produce detectable myocyte necrosis. Post-operative IMA increases are consistent with ischemic modification of albumin during exposure to ischemic conditions in skeletal muscle during and /or immediately after tourniquet application. However, the negative correlations between IMA and albumin results suggest that increases in IMA were in part due to lower post-operative albumin concentrations resulting in decreased cobalt binding.

Keywords: Albumin; Cobalt binding test; Skeletal muscle; Ischemia

1. Introduction

Ischemia, hypoxia, acidosis, and free radical formation can alter the ability of the first 3 amino acids in the albumin N-terminus, Asp–Ala–His, to bind free metal atoms including cobalt [1–4]. These modifications are transient, and albumin regains its cobalt binding capacity within 6 h [1,2,4].

Based on these biochemical changes, the albumin cobalt binding test (ACB®) (Inverness Medical Innovations Inc., Waltham, MA) was developed to quantify ischemia-modified albumin (IMA) in serum, with the intent of identifying patients with cardiac ischemia. Its use, in conjunction with ECG and cardiac troponin, has been suggested to be useful in evaluating patients presenting with symptoms of cardiac damage. When ACB® results were used in combination with an ECG and serial troponins, physicians were 70% accurate in ruling out cardiac ischemia. When using only ECG and troponin data, physicians' diagnostic accuracy decreased to 50% for ruling out ischemia [3,5].

Because ischemia, and the resulting biochemical changes that modify albumin, can occur in any vascular bed, the specificity of IMA for cardiac muscle ischemia is unclear [6–9] and requires further investigation. We evaluated the

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specificity of the ACB® test by measuring serum IMA concentrations in patients with skeletal muscle ischemia due to a pressurized tourniquet cuff during arthroscopic knee surgery.

2. Methods and materials

The study was approved by the Washington University School of Medicine IRB committee. Informed consent was obtained from patients undergoing elective arthroscopic knee surgery. Potential subjects were excluded from participation in the study if any of the following conditions were noted during pre-operative assessment: pregnancy, renal insufficiency, chronic liver disease, active cancer, acute chest pain, or a history of cardiovascular disease. Patients were instructed to stop eating and drinking at midnight prior to surgery the following morning. Intravenous hydration with lactated ringers was begun before surgery and discontinued at discharge (average 1.3 l). During surgery, a pressurized thigh cuff on the operative leg was continuously inflated to 300 mm Hg, in order to arrest blood flow during the procedure, until shortly before patients were transferred to the recovery room. Venous blood samples were collected via separate venipunctures into tubes prior to insertion of an intravenous catheter and within an hour before application of the pressure cuff, again within approximately 15 min of arrival in recovery, and finally, prior to discharge (range 1.0–3.25 h after arrival in recovery). Processing, aliquoting, and freezing of serum samples at − 80 °C for later testing were completed within 2 h of sample collection.

IMA was measured with the ACB® test adapted to a Roche/Hitachi MODULAR P instrument (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions and previous studies [2]. Within-assay ($n=10$) and between-assay ($n=2\times5$ days) imprecision (CV) was determined at IMA concentrations of 57, 78, and 124 KU/l, and was respectively <2.0% and <4.5% for each concentration.

Albumin concentrations were measured using the MODULAR P instrument and reagents (Roche). Myoglobin concentrations were measured using the Dade Dimension RxL instrument and reagents (Dade Behring Inc, Newark, DE) [10,11].

IMA concentration was modeled using mixed model analysis of variance (ANOVA). The model treated period (pre-operative, recovery, discharge) as a fixed effect, albumin concentration as a continuous covariate, and patients as a random sample (random effect). The model was used to estimate the patient's change in IMA

Table 1
Clinical characteristics of arthroscopic surgery patients ($n=19$)

Age (median)	33–79 (50)
Sex	M=9
	F=10
	Mean (SD)
Body surface area (m^2)	2.10 (0.25)
Pressurized cuff tourniquet (mm Hg)	300 (0)
	Range (median)
Tourniquet duration (min)	19–108 (29)
Cuff release to recovery (min)	7–32 (12)
Cuff release to discharge (min)	65–208 (136)

Table 2
Range, median, and P values of IMA, myoglobin, and albumin concentrations of pre-operative, recovery, and pre-discharge time points

	Range (median)	P value[a]
Myoglobin (ng/ml)		
Pre-operative	19–86 (37)	.....
Recovery	24–160 (47)	<0.001
Pre-discharge	24–139 (48)	0.0001
IMA (KU/l)		
Pre-operative	77–101.6 (90.2)	.....
Recovery	82.4–102.4 (97.1)	<0.005
Pre-discharge	81.8–113 (96.7)	<0.01
Albumin[b] (g/dl)		
Pre-operative	3.7–4.8 (4.45)	.....
Recovery	3.7–4.6 (4.20)	<0.05
Pre-discharge	3.4–4.6 (4.05)	<0.05

[a] P value, determined by sign-rank test, denotes statistical differences compared to pre-operative concentration.
[b] Albumin was measured in 14 patients.

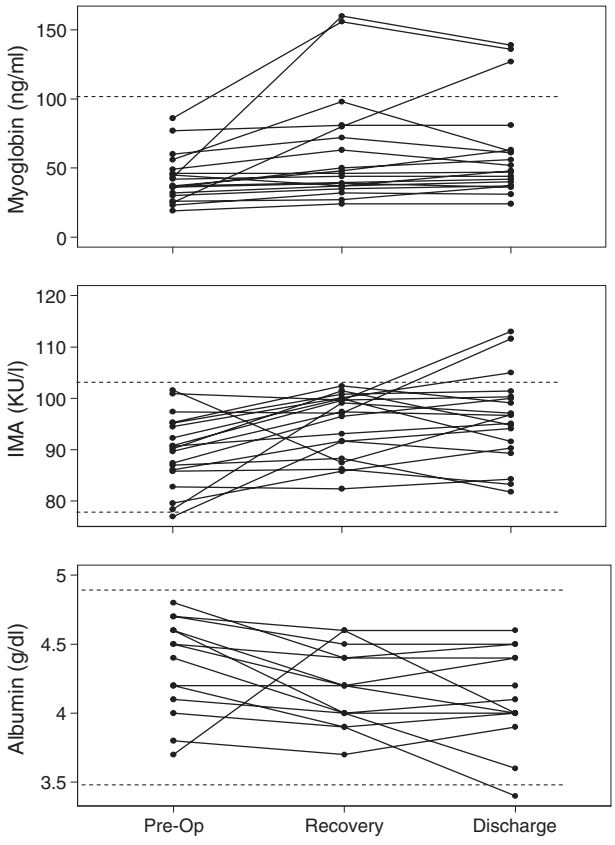

Fig. 1. Ischemic-modified albumin, myoglobin, and albumin concentrations at 3 different time periods; pre-operative, recovery, and discharge. Dotted lines indicate the normal reference interval for each analyte.