Serum Ischemia-modified Albumin Levels in an Experimental Acute Mesenteric Ischemia Model

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Abstract

Objectives: This experimental study aimed to assess the changes in the levels of serum ischemia-modified albumin (IMA) and interleukin-6 (IL-6) by time in cases of acute mesenteric ischemia due to superior mesenteric artery occlusion.

Methods: Twenty-one New Zealand rabbits were randomly divided into three groups. Blood samples were collected at hours 0, 1, 3, and 6 from animals in a control group; a sham group following a simple laparotomy; and in an ischemia group following superior mesenteric artery ligation. All blood samples were analyzed for serum IMA and IL-6 levels, and then the time-dependent changes of biomarkers were investigated.

Results: The serum IMA levels of the ischemia group at hours 3 and 6 were significantly higher than those of the control and sham groups (hour 3, $p = 0.017$; hour 6, $p = 0.001$). The increase in serum IL-6 levels in the ischemia group at hours 1, 3, and 6 compared to the control and sham groups was also significant (hour 1, $p = 0.002$; hour 3, $p = 0.003$; hour 6, $p = 0.003$).

Conclusions: IMA may be helpful as a marker in the diagnosis of acute mesenteric ischemia; however, its diagnostic value and use as a routine biochemical test should be assessed in further studies.

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Mesenteric ischemia is a sudden decrease in intestinal blood flow due to occlusion, vasospasm, or hypoperfusion.[1,2] Currently, acute mesenteric ischemia accounts for approximately 0.1% of all hospital admissions,[2] and while it constitutes 1% to 2% of all gastrointestinal diseases, the incidence has recently increased with the increasing age of the population.[3]

The mortality rate of acute mesenteric ischemia due to all causes is approximately 71%, with a range of 59% to 93%.[2–4] Early diagnosis, before the development of intestinal infarction and peritonitis, is essential for patient survival.[2,4] In a case series of 21 patients with embolism of the superior mesenteric artery, intestinal viability was found to be 100% in patients who were diagnosed within the first 12 hours of the onset of symptoms, 56% in those diagnosed within 12–24 hours, and 18% in those diagnosed after 24 hours.[5]

In acute mesenteric ischemia, for which time is vital according to the consensus result of recent studies on biochemical markers, there is no adequately sensitive and specific marker with an early diagnostic power to increase survival.[6] The optimum biochemical marker to be used in the early diagnosis of acute mesenteric ischemia should be released from the intestinal mucosa, should escape from the first-pass effect of the liver, and should be detected in the peripheral blood. The new diagnostic markers, which have recently been developed with this thought, are more promising than older markers.[6–8]

During ischemia or reperfusion after ischemia, the human serum albumin capacity for metal binding may decrease as a result of loss of a part of the N-terminal connection site of the albumin or significant molecular modification. This decrease in metal binding capacity can be measured and is known as ischemia-modified albumin (IMA). It has been suggested that these changes in human serum albumin, which occur as a result of ischemia reperfusion, are endothelial and extracellular hypoxia, acidosis, free radical damage,

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membrane energy–dependent sodium and calcium pump disorders, and exposure to free iron and copper.[9,10] In the literature, there are few studies on IMA levels in acute mesenteric ischemia: a pilot study including seven patients and a clinical study including 12 patients with the diagnosis of the intestinal ischemia.[11,12]

Interleukin-6 (IL-6) is a proinflammatory cytokine released from mononuclear phagocytes with various stimuli. It forms a systemic inflammatory response syndrome by neutrophil activation and endothelial intercellular adhesion molecule-1 up-regulation. The systemic release of tumor necrosis factor-α (TNF-α) and IL-6 are related to septic shock and fatal outcomes.[13] It has been found that TNF-α and IL-6 levels increased continuously after intestinal ischemia, and these cytokines are released from Kupffer cells.[14] In one clinical study, it was reported that serum IL-6 levels were useful in diagnosing patients with acute intestinal ischemia.[15]

In this experimental study, we aimed to assess the levels of serum IMA and IL-6 in acute mesenteric ischemia due to superior mesenteric artery occlusion. While prior human studies measured preoperative IMA and IL-6 levels, this complimentary animal model study was designed to demonstrate how soon IMA and IL-6 can rise after the artery occlusion.

METHODS

Study Design

This was an animal model laboratory study using rabbits. The Ethics Committee for Experimental Animal Studies of Selcuk University, Turkey, approved the experimental protocol.

Animal Subjects and Preparation

A total of 21 adult female New Zealand rabbits, with body weights ranging between 2500 and 3000 g, were used. All rabbits were kept in the same environment and feeding conditions. The rabbits were put through 12 hours of fasting before the experiment, and they were only allowed to drink water during this period.

Study Protocol

The rabbits were randomly placed into three groups of seven rabbits each. Following provision of anesthesia by 50 mg/kg ketamine and 15 mg/kg xylazine, a catheter was inserted in the dorsal ear vein of each rabbit. After obtaining each blood sample, 5 mL of saline was given through the same vein.

Control Group (Group I). Blood samples of 5 mL were obtained at hours 0, 1, 3, and 6 for biochemical assessment. No tissue specimens were obtained in this group.

Sham Group (Group II). Blood samples of 5 mL were obtained at hour 0 for biochemical assessment. After blood samples were obtained, the abdominal regions of the rabbits were shaved and cleaned with 10% povidone iodine. Laparotomy was performed through a midline incision. After passing through the peritoneum, the abdominal wall and the peritoneum were sutured with 2-0 silk suture material. Blood samples of 5 mL were obtained at hours 1, 3, and 6 postoperatively for biochemical analyses. No tissue specimens were obtained in this group.

Ischemia Group (Group III). Blood samples of 5 mL were obtained at hour 0 for biochemical assessment. After obtaining the blood samples, the abdominal regions of the rabbits were shaved and cleaned with 10% povidone iodine. Laparotomy was performed through a midline incision. The superior mesenteric artery was found and ligated with 0 silk sutures. The peritoneum and the abdominal wall were sutured with 2-0 silk suture. Blood samples of 5 mL were obtained at hours 1, 3, and 6 postoperatively for biochemical assessment. After 6 hours of ischemia, the rabbits were sacrificed with high-dose ketamine. The distal ileum specimen of 10 cm was washed with saline and placed in 10% formaldehyde solution for histopathologic examination.

Storing Specimens

Each blood sample of 5 mL in a gel-containing Vacutainer tube was centrifuged at 3,000 rpm for 10 minutes, after having waited 30 minutes for clotting. The sera were placed in Eppendorf tubes using a pipette. The samples were stored at –20°C until biochemical assessment. The distal ileum specimens were washed with saline and fixed with 10% formaldehyde solution for histopathologic examination and embedded in paraffin blocks after routine xylol-alcohol series.

Assessing the Specimens

Biochemical Assessment. An albumin-cobalt binding test was used to define serum IMA levels. The decreasing binding capacity of cobalt to albumin was assessed using the rapid colorimetric detection method developed by Bar-Or et al.[9] A sample of the rabbit serum (200 μL) was placed in an Eppendorf tube, and 50 μL of 0.1% $CoCl_2 \cdot 6H_2O$ was added. It was stirred slowly and then held for 10 minutes to allow binding of sufficient cobalt albumin; 50 μL of 1.5 mg/mL dithiothreitol (DTT) was added as a coloring agent. After 2 minutes, the reaction was stopped by adding 1 mL of 0.9% NaCl to the solution to stop the binding between cobalt and albumin. A set of blind specimens without DTT was prepared, with 50 μL of distilled water added instead of 50 μL of 1.5 mg/mL DTT. The specimen absorbents were measured at 470 nm in the spectrophotometer. The color formation in the specimens with DTT was compared to the color formation of the blind tubes, and the results were reported as absorbance units (ABSU). A relevant enzyme-linked immunosorbent assay (ELISA) kit (rabbit IL-6 ELISA kit, CSB-E06903Rb, Cusabio Biotech Co. Ltd., Newark, DE) was used to detect the serum IL-6 levels.

Histopathologic Assessment. Sections of 5 μm thickness were prepared from the tissue specimens embedded into paraffin blocks using a microtome. The specimens were stained by hematoxylin-eosin and examined under the microscope with 100× magnifications.

The mucosal damage was grouped according to the scoring system described by Chiu et al.[16] grade 0,

normal villus; grade 1, enlargement of the subepithelial area, capillary congestion in the villus apex; grade 2, subepithelial congestion expanding to the villus base; grade 3, ulceration in some villus apex, disseminated subepithelial congestion; grade 4, ulceration in the villus, dilated capillary in lamina propria; and grade 5, irregularity, hemorrhage, and ulceration in lamina propria.

Data Analysis

The data were analyzed using SPSS software (version 16.0, SPSS Inc., Chicago, IL). The comparison of groups was performed using the Kruskal-Wallis variance analysis and the Mann-Whitney U-test with Bonferroni correction. The changes of markers in time were assessed by the Friedman test and the Wilcoxon test with Bonferroni correction. The relationship between IMA and IL-6 levels was assessed using the Spearman correlation analysis.

RESULTS

Biochemical Markers

Serum IMA and IL-6 levels were measured in blood samples at hours 0, 1, 3, and 6 in all rabbits (n = 21). The serum IMA levels of the groups are presented in Table 1, and the change in time in serum IMA levels is presented in Figure 1. There was no significant difference between control, sham, and ischemia groups for the serum IMA levels at hours 0 and 1 ($p > 0.05$). The serum IMA levels of the ischemia group at hours 3 and 6 were significantly higher than those of the control and sham groups (hour 3, $p = 0.017$; hour 6, $p = 0.001$). The IMA levels of the ischemia group tended to rise continuously at hours 0, 1, 3, and 6, and this increase was significant ($p < 0.001$). There was no increase in the serum IMA levels of the sham group ($p > 0.05$).

Table 1
Serum IMA Levels (ABSU)

Group	Hour 0	Hour 1	Hour 3	Hour 6
Control				
Median	0.458	0.441	0.447	0.451
Percentile				
25th	0.387	0.376	0.393	0.372
50th	0.458	0.441	0.447	0.451
75th	0.488	0.487	0.500	0.499
Sham				
Median	0.460	0.457	0.468	0.477
Percentile				
25th	0.393	0.439	0.415	0.439
50th	0.460	0.457	0.468	0.477
75th	0.507	0.483	0.507	0.504
Ischemia*				
Median	0.470	0.484	0.523	0.720
Percentile				
25th	0.425	0.443	0.514	0.701
50th	0.470	0.484	0.523	0.720
75th	0.492	0.507	0.639	0.745

ABSU = absorbance unit; IMA = ischemia-modified albumin.
*p-values determined for the comparison of time-dependent IMA levels in the ischemia group; p = 0.017 for hour 3, p = 0.001 for hour 6.

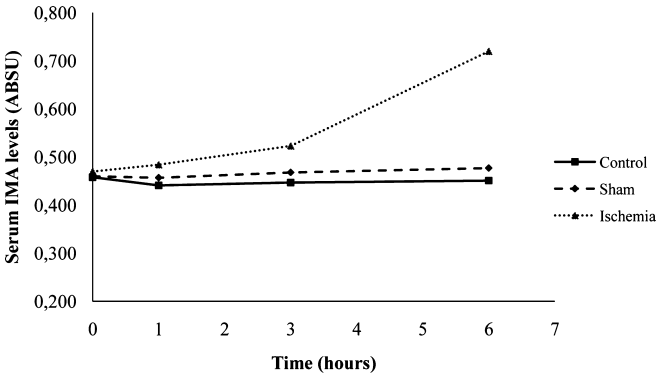

Figure 1. Time-dependent changes of serum IMA levels. ABSU = absorbance unit; IMA = ischemia modified albumin.

Table 2
Serum IL-6 Levels (pg/mL)

Group	Hour 0	Hour 1	Hour 3	Hour 6
Control				
Median	20	11	21	19
Percentile				
25th	0	0	0	0
50th	20	11	21	19
75th	68	58	51	76
Sham				
Median	20	19	49	24
Percentile				
25th	0	0	0	0
50th	20	19	49	24
75th	78	63	76	76
Ischemia*				
Median	23	209	644	818
Percentile				
25th	0	179	462	794
50th	23	209	644	818
75th	60	251	694	1020

IL-6 = interleukin-6
*p-values determined for the comparison of time-dependent IL-6 levels in the ischemia group; p = 0.002 for hour 1, p = 0.003 for hour 3, p = 0.003 for hour 6.

The serum IL-6 levels of the groups are presented in Table 2, and the change of serum IL-6 levels by time shown in Figure 2. There was no significant difference between the control, sham, and ischemia groups for the serum IL-6 levels at hour 0 ($p > 0.05$). The increase in serum IL-6 levels in the ischemia group at hours 1, 3, and 6 compared to the control and sham groups was significant (hour 1, $p = 0.002$; hour 3, $p = 0.003$; hour 6, $p = 0.003$). The IL-6 levels in the ischemia group at hours 0, 1, 3, and 6 tended to increase continuously, and this increase was significant ($p < 0.001$). The relationship between serum IMA and IL-6 levels in the ischemia group was assessed, and a significant positive correlation was found ($R^2 = 0.67$, $p < 0.001$; Figure 3).

Histopathologic Assessment

Microscopic evaluation revealed villus ulceration, dilated capillaries in the lamina propria (grade 4) and irregularity, hemorrhage, and ulceration in the lamina propria (grade 5; n = 2).

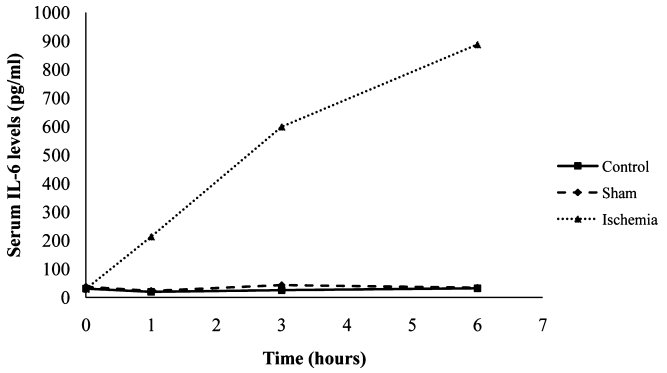

Figure 2. Time-dependent changes of serum IL-6 levels. IL-6 = interleukin-6.

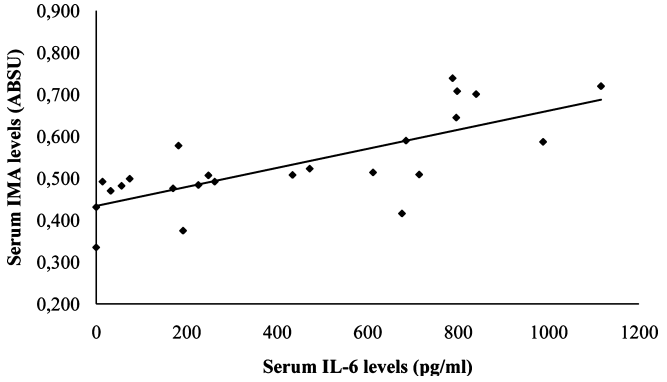

Figure 3. The relationship between serum IMA and IL-6 levels in the ischemia group. (R^2 = 0.67, p<0.001). IMA = ischemia-modified albumin; ABSU = absorbance unit; IL-6 = interleukin-6.

DISCUSSION

Mesenteric ischemia is a disease with lower prevalence but higher mortality rates compared to most other causes of abdominal pain at the ED; therefore, it requires a fast diagnosis. Diagnosis can be difficult due to subtle and nonspecific clinical findings and limited diagnostic tests.[17–19]

In acute ischemic conditions, the metal (such as copper, cobalt, and nickel) binding capacity of albumin in the N-terminal zone is decreased. This decrease can be measured and is known as IMA.[9,11] Studies have recently been conducted on elevated levels of IMA in ischemic conditions including pulmonary embolism, acute coronary syndrome, cerebrovascular accidents, and deep venous thrombosis.[11,20–22]

In a pilot study of seven patients with the diagnosis of acute mesenteric ischemia, IMA levels were found to be significantly higher than those of the healthy control group.[11] In another clinical study, IMA levels were measured in 26 patients, including 12 with the diagnosis of intestinal ischemia. It was reported in this study that IMA levels were significantly higher in cases with the diagnosis of intestinal ischemia.[12]

There is one experimental study in the literature in which IMA levels were assessed in acute mesenteric ischemia. In this study of rats, IMA levels were assessed at 30 minutes, 2 hours, and 6 hours after ligation of the superior mesenteric artery, and it was reported that IMA levels increased as the duration of ischemia increased. In the same study, in a sham group in which the abdominal wall was just opened and closed, IMA levels were found to be elevated, although to a lower extent than the ischemia group.[23] In our study we found that serum IMA levels increased in the ischemia group at hours 1, 3, and 6 after superior mesenteric artery occlusion. Our data show that IMA levels increase significantly as the ischemia time prolongs, and this result is consistent with that of the literature. Different from the literature, in our study, although the IMA levels showed a continuous increase with time in the ischemia group, there was no significant difference at one hour of ischemia between the sham and the ischemia groups.

Although we are aware of no prior studies of IMA levels in a rabbit model of acute mesenteric ischemia, an experimental study with rabbits demonstrated that serum IMA levels increased at hours 1, 3, and 6 in a pulmonary embolism model.[24] In our study, we measured serum IMA levels at hours 0, 1, 3, and 6 after intestinal ischemia, and a statistically significant increase in IMA levels was observed. Conducting the study on rabbits enabled us to obtain blood samples from the same subject and thus enabled us to assess the effect of ischemia time on IMA levels more accurately. We were able to assess the effect of repetitive blood sampling on serum IMA and IL-6 levels by using the control group.

It is important to have a less invasive, rapid, and efficient method in the diagnosis of acute mesenteric ischemia. Determining a rapid biochemical marker from an easily available sample such as venous blood will be an important step in the mortality and morbidity of acute mesenteric ischemia. The encouraging aspects of this marker in the diagnosis of acute mesenteric ischemia are the chance of studying IMA in blood samples, elevation in ischemic events, and having a study protocol lasting approximately 10–15 minutes.

We also investigated serum IL-6 levels in acute mesenteric ischemia. We found that serum IL-6 levels significantly increased in blood, starting from the first hour of ischemia. In a clinical study, IL-6 levels were measured in a total of 46 patients presenting to the ED with acute abdomens, and it was reported that serum IL-6 levels were significantly increased in patients with acute intestinal ischemia.[15] In another study, the effects of acute transient intestinal ischemia in 15 patients undergoing elective open surgery for the treatment of abdominal subrenal aortic aneurysm induced by clamping of the aorta above the branching of the inferior mesenteric artery for 75 minutes were investigated, and it was reported that serum IL-6 levels were significantly elevated in the ischemic phase.[25] Our results are consistent with that literature.

When the pathophysiology of local and distant organ damage is assessed in acute mesenteric ischemia, a systemic inflammatory response syndrome and septic complications occur almost in every case. The high mortality rate in mesenteric ischemia is usually related to these septic complications.[26,27] The increase in blood IL-6 level is also valuable for the demonstration of the

emergence of the systemic response in the early stages of ischemia and for the assessment of the clinical status of patients.

We are aware of only one study that has compared the IMA levels and the other markers in acute mesenteric ischemia. In this study with rats, the relationships between the levels of IMA and of lactate and malondialdehyde, which are markers of ischemia, were assessed. It was reported that there was a positive correlation between the blood levels of IMA and lactate and malondialdehyde.[23] In our study, we examined the relationship with IL-6 (which is a proinflammatory cytokine) and IMA in acute mesenteric ischemia progress and found a positive correlation between serum IMA and IL-6 levels.

LIMITATIONS

Our study was designed to investigate the changes in serum IMA and IL-6 levels by time in cases of acute mesenteric ischemia due to superior mesenteric artery occlusion, but different causes of mesenteric ischemia may show different marker responses. We did not compare IMA and IL-6 levels with other biomarkers already investigated in the diagnosis of mesenteric ischemia.

Further studies are required to find the changes in the blood levels of IMA and IL-6 in other causes of abdominal pain and to decide the adequacy of specificity. Also, it is well known that IMA levels are elevated in essentially all ischemic events. The diagnostic value of serum IMA levels should be investigated in studies with various designs, especially if the physical examination findings are subtle in the clinical picture of acute mesenteric ischemia presenting with concurrent multiembolic conditions such as pulmonary embolism, ischemic cerebrovascular events, acute coronary syndrome, and deep venous thrombosis.

CONCLUSIONS

Ischemia-modified albumin may be helpful as a marker in the diagnosis of acute mesenteric ischemia; however, its diagnostic value and use as a routine biochemical test should be assessed in further studies.

References

1. Boley SJ, Brandt LJ, Sammartano RJ. History of mesenteric ischemia. Surg Clin North Am. 1997; 77:275–88.
2. Stamatakos M, Stefanaki C, Mastrokalos D, et al. Mesenteric ischemia: still a deadly puzzle for medical community. Tohoku J Exp Med. 2008; 216:197–204.
3. Yasuhara H. Acute mesenteric ischemia: the challenge of gastroenterology. Surg Today. 2005; 35:185–95.
4. American Gastroenterology Association. Technical review on intestinal ischemia. Gastroenterology. 2000; 118:954–68.
5. Lobo Martinez E, Merono Carvajosa E, Sacco O, Martinez Molina E. Embolectomy in mesenteric ischemia. Rev Esp Enferm Dig. 1993; 83:351–4.
6. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009; 33:1374–83.
7. Block T, Nilsson TK, Björck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. Scand J Clin Lab Invest. 2008; 68:242–8.
8. Glinester KM, Corke CF. Infarcted intestine: a diagnostic void. ANZ J Surg. 2004; 74:260–5.
9. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000; 19:311–5.
10. Lippi G, Montagnana M, Guidi GC. Albumin cobalt binding and ischemia modified albumin generation: an endogenous response to ischemia? Int J Cardiol. 2006; 108:410–1.
11. Gunduz A, Turedi S, Mentese A, et al. Ischemia modified albumin in the diagnosis of acute mesenteric ischemia: a preliminary study. Am J Emerg Med. 2008; 26:202–5.
12. Polk JD, Rael LT, Craun ML, Mains CW, Davis-Merritt D, Bar-Or D. Clinical utility of the cobalt-albumin binding assay in the diagnosis of intestinal ischemia. J Trauma. 2008; 64:42–5.
13. Marshall JC, Vincent JL, Fink MP, et al. Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25–26, 2000. Crit Care Med. 2003; 31:1560–7.
14. Towfigh S, Heisler T, Rigberg DA, et al. Intestinal ischemia and the gut-liver axis: an in vitro model. J Surg Res. 2000; 88:160–4.
15. Sutherland F, Cunningham H, Pontikes L, Parsons L, Klassen J. Elevated serum interleukin 6 levels in patients with acute intestinal ischemia. Hepatogastroenterology. 2003; 50:419–21.
16. Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surg. 1970; 101:478–83.
17. Chang JB, Stein TA. Mesenteric ischemia: acute and chronic. Ann Vasc Surg. 2003; 17:323–8.
18. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004; 164:1054–62.
19. Ujiki M, Kibbe MR. Mesenteric ischemia. Perspect Vasc Surg Endovasc Ther. 2005; 17:309–18.
20. Mentese A, Mentese U, Turedi S, et al. Effect of deep vein thrombosis on ischemia modified albumin levels. Emerg Med J. 2008; 25:811–4.
21. Abboud B, Labreuche J, Meseguer E, et al. Ischemia modified albumin in acute stroke. Cerebrovasc Dis. 2007; 23:216–20.
22. Cho DK, Choi JO, Kim SH, et al. Ischemia modified albumin is a highly sensitive serum marker of transient myocardial ischemia induced by coronary vasospasm. Coron Artery Dis. 2007; 18:83–7.
23. Gunduz A, Turkmen S, Turedi S, et al. Time-dependent variations in ischemia modified albumin levels in mesenteric ischemia. Acad Emerg Med. 2009; 16:539–43.

24. Turedi S, Patan T, Gunduz A, et al. Ischemia modified albumin in the diagnosis of pulmonary embolism: an experimental study. Am J Emerg Med. 2009; 27:635–40.
25. Lammers KM, Innocenti G, Venturi A, et al. The effect of transient intestinal ischemia on inflammatory parameters. Int J Colorectal Dis. 2003; 18:78–85.
26. Abboud B, Daher R, Boujaoude J. Acute mesenteric ischemia after cardiopulmonary bypass surgery. World Gastroenterol. 2008; 14:5361–70.
27. Cerqueira NF, Hussni CA, Yoshida WB. Pathophysiology of mesenteric ischemia/reperfusion: a review. Acta Cir Bras. 2005; 20:336–43.

Call for Papers
2011 Academic Emergency Medicine Consensus Conference
Interventions to Assure Quality in the Crowded Emergency Department

The 2011 *Academic Emergency Medicine* Consensus Conference "*Interventions to Assure Quality in the Crowded Emergency Department*" will be held on June 1, 2011, immediately preceding the SAEM Annual Meeting in Boston, Massachusetts. Original papers on the conference topic, if accepted, will be published together with the conference proceedings in the December 2011 issue of *Academic Emergency Medicine*.

The Institute of Medicine's (IOM) Committee on the Future of Emergency Care characterized hospital-based emergency care in the US as "at the breaking point." Many emergency departments (EDs) face frequent and prolonged periods of crowding because of mismatches between capacity and demand for services. Several studies have found that ED crowding delays the timeliness of emergency care. Studies have also demonstrated the negative effect of crowding on the other dimensions of quality including safety, effectiveness, efficiency, equity, and patient-centeredness.

System-wide constraints and/or inefficiencies in the ED and the hospital, including the lack of bed availability, cause ED crowding. Therefore, system-wide solutions are needed at the ED, hospital, community, and national levels. Some EDs and hospitals have experimented with different strategies (e.g. staffing, communication, information technology, etc) to safeguard the quality of emergency care during capacity-constrained periods. The main focus of the conference will be to develop a research agenda to study interventions aimed at improving ED and hospital flow. However, attention will also be paid to public policy or health care reform changes that may influence crowding and the quality of emergency care.

The specific goals of the consensus conference are:
1. **To develop a research agenda that identifies promising interventions that safeguard one or more of the six IOM domains of quality of care during crowded periods in the ED;**
2. To review interventions that have been implemented to reduce crowding and summarize the evidence of their impact on the delivery of emergency care;
3. To identify methodological challenges associated with the implementation and evaluation of interventions designed to safeguard the quality of emergency care during crowded periods; and
4. To identify policy strategies as well as strategies used by other industries to optimize system performance and determine their applicability to solving quality of care problems associated with crowding in the ED.

Interventional research aimed at assuring quality of care during crowded periods may address any of the above objectives. Examples of research topics that would qualify include:
- Studies that seek hospital-wide solutions to crowding in the ED;
- Policy solutions (e.g. four hour rule in the United Kingdom or pay-for performance in Ontario, Canada);
- Information technology interventions that may be used to warn ED providers or administrators that conditions in the ED have reached an unsafe threshold;
- Interventions that enhance ED throughput (efficiency and timeliness); and
- Interventions that inform patients about delays in care and evaluate their impact on patient satisfaction (patient-centered care).

Original contributions describing relevant research or concepts in this topic will be considered for publication in the December 2011 special topics issue of *AEM* if received by Monday, March 28, 2011. All submissions will undergo peer review, and publication cannot be guaranteed. For queries, please contact Melissa McCarthy, ScD (mmccarth@jhmi.edu) or Jesse Pines, MD (jesse.pines@gmail.com), Consensus Conference Co-Chairs. Information and updates will also be posted in the SAEM newsletter and the *AEM* and SAEM websites.