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Cardiac Isoenzyme Values After Total Joint Arthroplasty

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→ The purpose of this study was to prospectively determine what effect total joint arthroplasty had on the myocardial-associated isoenzymes of serum creatine kinase (CK-MB) and lactate dehydrogenase (LD-1:LD-2). Fifty patients treated with total joint arthroplasty of the hip or knee had isoenzyme determinations using automated spectrophotometry and agarose gel electrophoresis. Skeletal muscle injury associated with the trauma of surgery resulted in significant elevations of the absolute value of CK-MB; however, the percentage of CK-MB comprising total CK activity and LD-1:LD-2 did not rise significantly in patients who did not experience postoperative myocardial infarction. It is important to determine both serum CK-MB and LD-1:LD-2 in suspected postoperative myocardial infarction since false positive elevations of CK-MB can occur. Elevations of CK-MB exceeding 50 International Units/liter or 5% of the total CK activity combined with LD-1:LD-2 exceeding 1.0 should not be attributed to skeletal muscle injury alone following total joint arthroplasty of the hip or knee. *Keywords:*

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Perioperative cardiovascular complications following total joint arthroplasty of the hip or knee have been reported to occur in 0.5%–5.0% of patients.^{3–6,10,11,15,21,24,29,31–34} Since well over 100,000 total joint arthroplasties of the hip or knee are performed annually in the United States, the number of perioperative cardiovascular complications is significant.¹⁹ Recent studies of noncardiac surgical patients (including orthopedic patients) found that postoperative myocardial infarction was associated with a 25%–43% incidence of cardiac death.^{1,12} Therefore, early accurate diagnosis of perioperative myocardial infarction is paramount since the classic presentation may be masked by postoperative pain, medications, or noncardiac complications.

Serum lactic dehydrogenase (LD), creatine kinase (CK), and their isoenzymes are used routinely to diagnose acute myocardial infarction in nonsurgical patients.^{8,13,23} It is well known that surgical manipulation of skeletal muscle causes elevation of serum total LD and CK; however, the effect of total joint arthroplasty on these enzymes and their isoenzymes has not been studied in detail.^{2,9,16} The purpose of this prospective study was to determine what effect total joint arthroplasty of the hip or knee has on these enzymes in patients who have not experienced acute perioperative myocardial infarction.

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MATERIALS AND METHODS

The protocol for this prospective study was approved by the Department of Clinical Investigation and the Human Use Committee at the authors' institution prior to obtaining any samples from patients. Fifty patients treated with total joint arthroplasty of the hip or knee were included in this study. Twenty-five patients ranging in age from 42 to 89 years were treated with 25 total hip arthroplasties, while 25 patients ranging in age from 41 to 81 years were treated with 27 total knee arthroplasties (two patients had staged bilateral total knee arthroplasties). All arthroplasties were primary except for one hip revision and one knee revision. All primary total hip arthroplasties were performed through a posterior approach, and the one total hip revision was performed through a transtrochanteric approach. All total knee arthroplasties were performed through a medial parapatellar approach that was extended proximally and distally.¹⁸ Twenty-three of the 50 patients (45%) were older than 70 years of age. All 52 joint arthroplasties were performed electively as either the first (approximate starting time, 9 AM) or second (approximate starting time, 12 noon) case of the day.

Each patient had 7 mm of peripheral venous blood drawn preoperatively and on postoperative Day 1 (15–18 hours postoperative), Day 2 (39–42 hours postoperative), and Day 3 (63–66 hours postoperative). All blood was drawn between 6 AM and 8 AM each day. These particular times were chosen because maximal elevations of serum CK occur within 24 hours following myocardial infarction, while maximum elevations of LD occur on Day 3 and later following infarction. The peak incidence of postoperative myocardial infarction occurs by postoperative Day 3.⁸ Total serum CK and LD were determined by automated spectrophotometry using the Encore Pipettor 2000 (Baker Instruments, Allentown, Pennsylvania). Only reagents and controls specific for use with this system were used for the analysis.^{22,27} Absolute values for total CK and LD were recorded in International Units/liter (IU/l). The serum isoenzymes of CK (CK-MM, CK-MB, CK-BB) and LD (LD-1 to LD-5) were determined by agarose gel electrophoresis using the Corning agarose clinical isoenzyme system (Corning, New York).^{17,26,30,35} Only Corning controls and reagents specific for this system were used in the analysis. The isoenzymes were recorded as the percentage of that particular isoenzyme comprising total enzyme activity. Absolute values in IU/l for each isoenzyme were then calculated by multi-

plying the total enzyme activity by the percentage of that particular isoenzyme. The specific methodology used in the authors' laboratory has recently been published.¹³ The ratio of LD-1 to LD-2 was also calculated on all samples since a value for this determination exceeding 1.0 suggests myocardial injury.^{9,13,23}

Each of the 50 patients had resting 12-lead electrocardiograms performed preoperatively and immediately postoperatively in the recovery room. All electrocardiograms were interpreted by one cardiologist who was unaware of the results of the enzyme studies. Acute perioperative myocardial infarction was diagnosed if there were classic electrocardiographic changes or if serum isoenzymes indicated myocardial injury.²⁸ For the purpose of this study, enzymatic diagnosis of myocardial infarction was defined by an absolute value of CK-MB exceeding 50 IU/l and LD-1:LD-2 greater than 1.0.^{13,14} These values have been used previously in studies of perioperative myocardial infarction in the authors' laboratory. Preoperative values were compared to postoperative values (preoperative *versus* postoperative Day 1 (POD1), preoperative *versus* POD2, and preoperative *versus* POD3) using the paired Student's *t*-test to determine statistical significance. Increases in total CK and total LD were compared to respective enzyme samples using the two-sample *t*-test to determine statistical significance.⁷

RESULTS

TOTAL HIP ARTHROPLASTY

There were 25 preoperative samples and 75 postoperative samples. The mean total serum LD was not significantly elevated postoperatively, although the elevations on POD1 suggest a difference (Tables 1 and 2, Fig. 1). The mean percentages of LD-1–LD-4 isoenzymes were not significantly different from baseline samples; however, LD-5 was significantly elevated on POD1 ($p < 0.025$). The mean postoperative LD-1:LD-2 ratios on POD1, POD2, and POD3 were not significantly different from preoperative values (Fig. 2). The mean values of the serum total CK and of the CK-MM isoenzyme were significantly elevated through POD3 ($p < 0.0005$). The mean value of CK-MB was

TABLE 1. The Values of Serum Isoenzyme LD in Patients Treated with Total Joint Arthroplasty

	Total LD (IU/l)	LD-1	LD-2	LD-3	LD-4	LD-5	LD-1:LD-2
THA patients							
Preop.	198 ± 23	18.5 ± 1.4	26.0 ± 1.1	20.9 ± 0.6	13.0 ± 0.6	21.0 ± 2.0	0.73 ± 0.04
POD1	227 ± 23	17.7 ± 1.8	23.4 ± 1.0	19.3 ± 0.8	13.4 ± 0.8	25.6 ± 1.5	0.77 ± 0.09
POD2	212 ± 30	20.3 ± 1.4	27.1 ± 1.1	19.9 ± 0.8	11.8 ± 0.7	21.6 ± 1.6	0.76 ± 0.06
POD3	187 ± 26	21.6 ± 1.2	28.0 ± 1.1	19.9 ± 0.6	11.3 ± 0.6	18.7 ± 1.4	0.77 ± 0.04
TKA patients							
Preop.	235 ± 37	21.6 ± 0.9	26.9 ± 1.1	19.7 ± 0.7	12.8 ± 0.7	18.9 ± 1.4	0.84 ± 0.05
POD1	336 ± 50	18.6 ± 1.2	25.0 ± 0.8	19.6 ± 0.6	13.6 ± 0.7	23.2 ± 1.3	0.75 ± 0.05
POD2	289 ± 52	18.3 ± 1.2	26.5 ± 1.3	19.4 ± 0.8	12.0 ± 0.6	23.7 ± 2.1	0.69 ± 0.03
POD3	251 ± 37	19.9 ± 1.2	28.3 ± 1.2	18.7 ± 0.9	12.6 ± 0.8	20.4 ± 1.4	0.73 ± 0.06

Values of isoenzymes are percentages ± SEM.

significantly elevated on POD1 ($p < 0.005$) and POD2 ($p < 0.05$), but not on POD3 (Fig. 3). The mean value of CK-BB was not significantly elevated on any of the three postoperative days. The mean percentages of CK-MM, CK-MB, and CK-BB were not significantly different on POD1-POD3. Eight of 75 postoperative samples (taken from six patients) had LD-1:LD-2 exceeding 1.0; however, none of these patients had absolute CK-MB values exceeding 18 IU/l. The maximum CK-MB value in any of the patients was 32 IU/l.

TOTAL KNEE ARTHROPLASTY

There were 27 preoperative and 81 postoperative samples. The mean serum total LD was significantly elevated on POD1 ($p < 0.001$) and POD2 ($p < 0.05$), but not on POD3 (Tables 1 and 2, Fig. 1). The mean percentages of LD-1-LD-4 isoenzymes were not significantly elevated; however, LD-5 was significantly elevated on POD1 ($p < 0.025$) and POD2 ($p < 0.01$). The mean LD-1:LD-2 never rose significantly and, in fact, was significantly lower on POD2 (p

TABLE 2. The Values of Serum Isoenzyme CK in Patients Treated with Total Joint Arthroplasty

	Absolute values (IU/l)				Percentages		
	TOTAL CK	CK-MM	CK-MB	CK-BB	CK-MM	CK-MB	CK-BB
THA patients							
Preop.	66 ± 8.4	63.5 ± 8.4	1.7 ± 0.5	0.8 ± 0.4	96.7 ± 1.0	1.9 ± 0.5	1.4 ± 0.5
POD1	427 ± 54.8	416.2 ± 54.6	7.8 ± 1.7	3.0 ± 2.6	97.4 ± 0.7	1.9 ± 0.4	0.7 ± 0.6
POD2	341 ± 48.2	333.6 ± 47.7	4.4 ± 1.3	3.0 ± 2.4	97.6 ± 1.2	1.5 ± 0.4	0.9 ± 0.9
POD3	220 ± 29.0	217.5 ± 28.8	1.8 ± 0.6	0.7 ± 0.5	98.9 ± 0.4	0.7 ± 0.2	0.4 ± 0.3
TKA patients							
Preop.	50 ± 4.7	48.1 ± 5.7	1.4 ± 0.4	0.5 ± 0.3	97.1 ± 1.1	2.0 ± 0.9	0.9 ± 0.5
POD1	125 ± 17.8	119.3 ± 17.6	4.6 ± 2.0	1.1 ± 0.6	95.7 ± 1.4	3.3 ± 1.3	1.0 ± 0.4
POD2	158 ± 25.4	153.9 ± 25.1	3.4 ± 1.1	0.7 ± 0.3	96.6 ± 1.3	2.6 ± 1.0	0.8 ± 0.5
POD3	101 ± 14.6	98 ± 14.6	2.0 ± 0.7	1.0 ± 0.6	96.5 ± 1.4	2.5 ± 1.3	1.0 ± 0.4

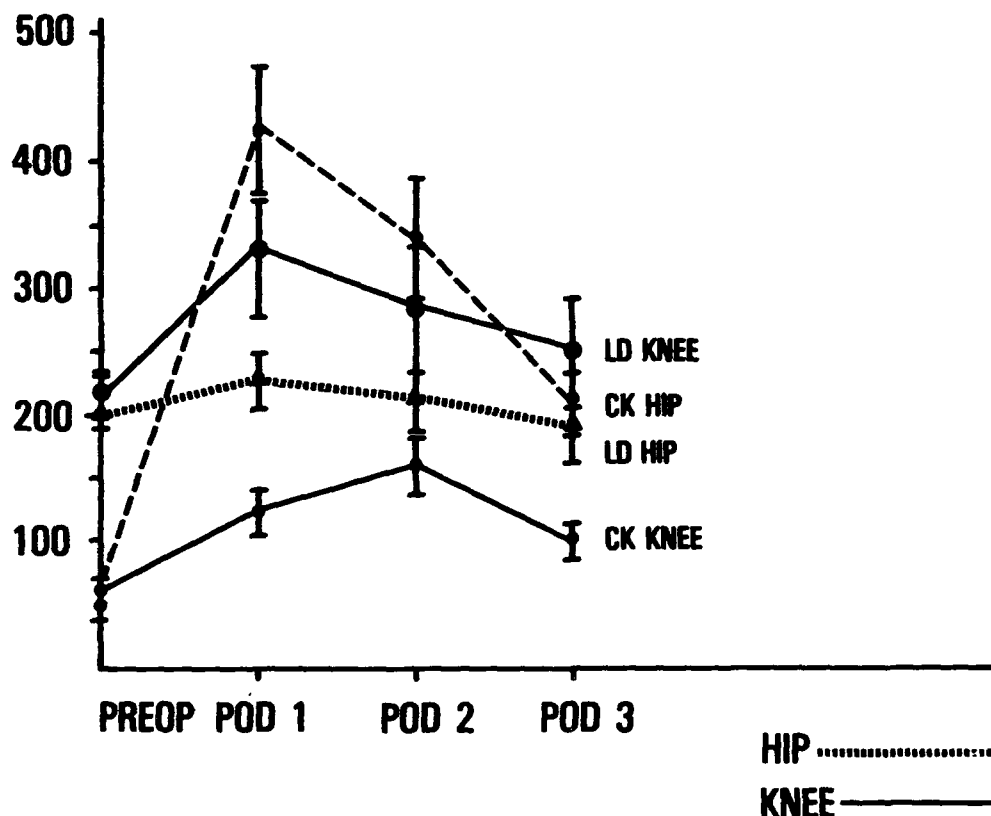


FIG. 1. The relationship of total CK and LD following total joint arthroplasty of the hip and knee.

< 0.005; Fig. 2). The mean absolute values of total serum CK and CK-MM were significantly elevated on POD1 ($p < 0.0005$), POD2 ($p < 0.0005$), and POD3 ($p < 0.005$). The mean value of CK-MB was significantly elevated on POD1 ($p < 0.05$), but not on POD2 or POD3 (Fig. 3). The mean absolute values of CK-BB were not significantly elevated on POD1-POD3. The mean percentages of CK-MM, CK-MB, and CK-BB were not significantly elevated on POD1-POD3. Six of 81 postoperative samples (five patients) had LD-1:LD-2 exceeding 1.0; however, none of these patients had CK-MB absolute values exceeding 13 IU/l. The maximum absolute CK-MB value was 52 IU/l. This patient did not experience any signs or symptoms of myocardial infarction and the postoperative electrocardiogram was un-

changed from the preoperative electrocardiogram. LD-1:LD-2 never exceeded 1.0 in this patient.

The elevations of total serum CK activity were significantly higher following total hip arthroplasty when compared to total knee arthroplasty on POD1 ($p < 0.0005$), POD2 ($p < 0.005$), and POD3 ($p < 0.0005$). Total mean LD elevation was significantly greater following total knee arthroplasty on POD1 ($p < 0.05$), but not on POD2 or POD3.

Three patients in this study group experienced postoperative chest pain and had electrocardiographic changes consistent with myocardial ischemia (electrocardiographic changes all resolved within 24 hours). Each patient had one sample with LD-1:LD-2 greater than 1.0; however, the maximum CK-MB value noted was only 13 IU/l.

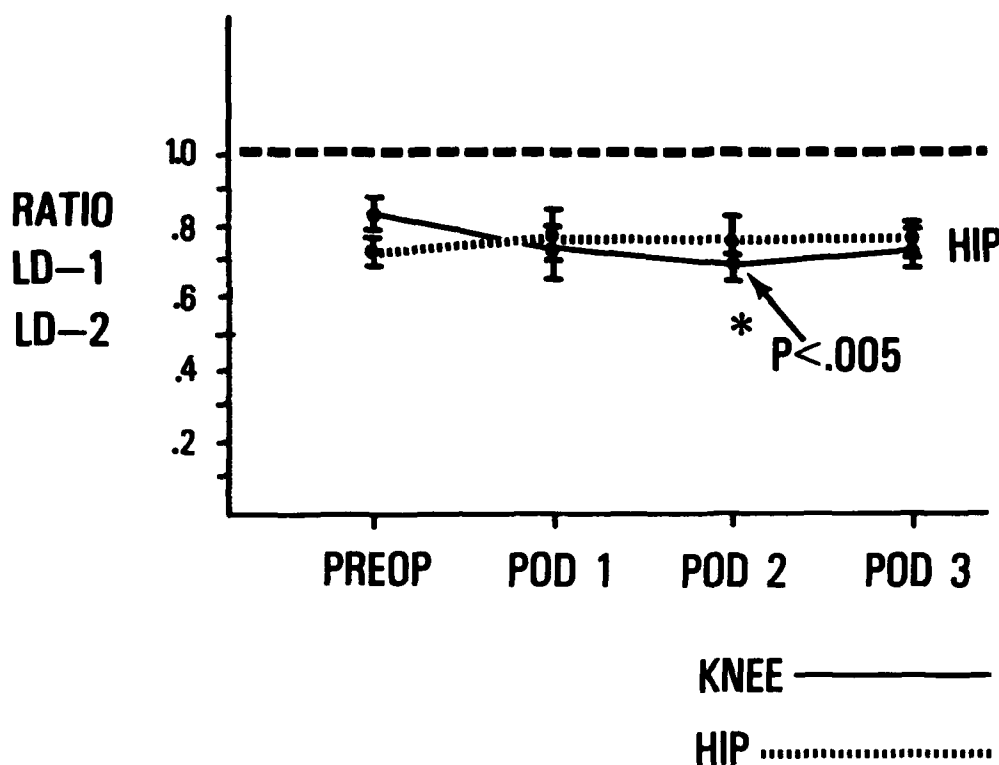


FIG. 2. LD-1:LD-2 following total joint arthroplasty of the hip and knee.

DISCUSSION

The diagnosis of acute myocardial infarction is made by history, physical examination, electrocardiographic changes, and determinations of serum enzymes.^{28,36} The history and physical examination are not specific for myocardial infarction since non-cardiac complications such as pulmonary embolism may accompany chest pain, dyspnea, and changes in vital signs.^{23,36} In addition, postoperative myocardial infarction can be painless in up to 50% of patients.⁷

Electrocardiograms, while specific in detecting transmural infarction, have been reported to be only 73% sensitive.²² A post-mortem study also reported that 30% of patients who had autopsy-proven myocardial infarctions had normal electrocardiograms.²⁰ Therefore, the diagnosis of postoperative myocardial infarction may depend on the

results of serum CK, LD, and isoenzyme determinations.

Creatine kinase is found primarily in skeletal muscle, myocardium, and brain, while smaller amounts can also be found in lung, bladder, and bowel. Three isoenzymes (CK-MM, CK-MB, and CK-BB) have been identified by electrophoresis. Skeletal muscle is comprised mainly of CK-MM, while myocardium is comprised of 25%–40% CK-MB.⁹ The CK-MB isoenzyme is virtually specific for myocardium. Galen^{8,9} reported that its presence in the serum is indicative of myocardial damage. Other studies have demonstrated that detectable amounts of CK-MB can be found in the serum of postoperative patients who have not experienced acute myocardial infarction.^{13,16,22} CK-BB can also be detected in the peripheral serum of postoperative patients.¹³

Lactate dehydrogenase is found in many

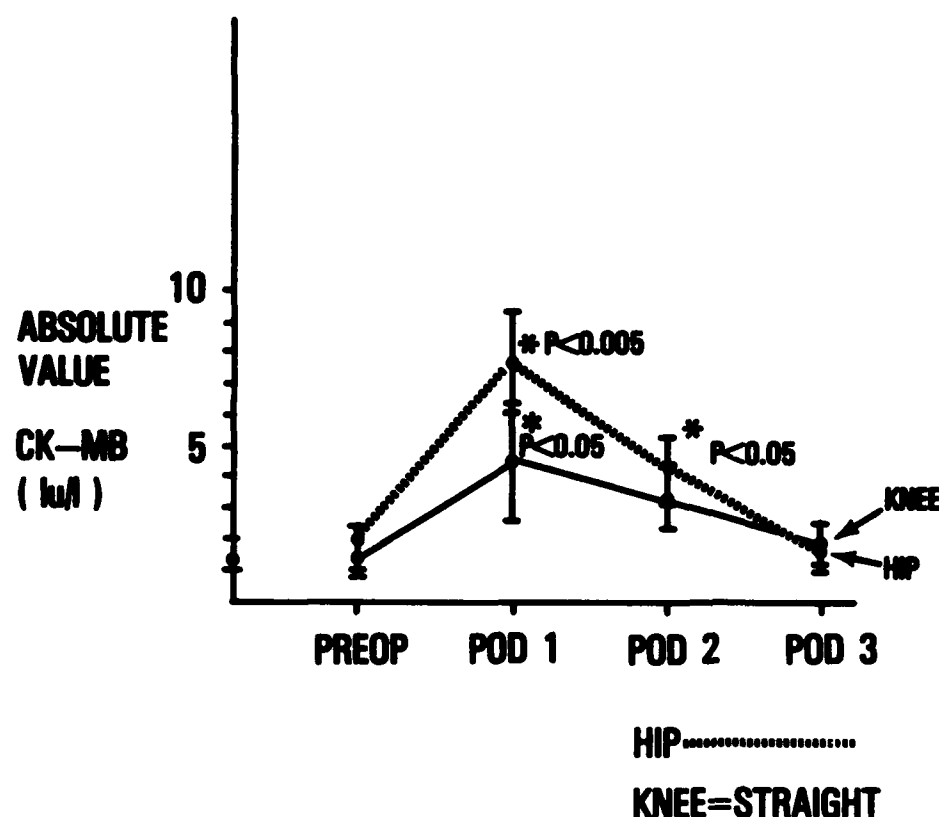


FIG. 3. The absolute values of myocardial-associated isoenzyme CK-MB following total joint arthroplasty of the hip and knee.

organs including myocardium, brain, kidney, lung, thyroid, bladder, uterus, bowel, spleen, liver, erythrocytes, and skeletal muscle.⁹ Five isoenzymes of LD have been identified by electrophoresis (LD-1-LD-5). The LD-1 isoenzyme comprises 40% of myocardial LD; however, LD-1 is not specific for myocardium since kidney, brain, and erythrocytes also have significant LD-1 activity.^{8,9} Skeletal muscle is comprised of 60% LD-5 and has virtually no LD-1 activity.^{8,9} In normal serum, LD-2 predominates and LD-1:LD-2 is less than 1.0.^{8,23}

Experimental and clinical studies have demonstrated that following acute myocardial infarction, total serum CK rises and the myocardial-associated isoenzyme, CK-MB, appears in the serum within six hours after the onset of symptoms.²³ Peak values are ob-

tained between 18 and 24 hours after infarction.^{9,13,23} In nonsurgical patients, CK-MB exceeding 5% of total serum CK is indicative of myocardial injury.^{9,23} LD-1 is also released into the serum following myocardial infarction resulting in LD-1:LD-2 greater than 1.0 (flipped LD pattern).^{9,13,23} The only other clinical situations that can result in a flipped LD pattern are hemolysis and renal infarction.⁸ Graeber¹³ found the sensitivity and specificity to be 99.9% in detecting myocardial infarction if two separate serum samples between 24 and 48 hours after surgery had both a flipped LD pattern and an absolute CK-MB value exceeding 50 IU/l. In postoperative patients, the absolute value of CK-MB may be a more reliable index of myocardial injury than the percentage of CK-MB for several reasons. First, a percent-

age does not indicate the amount of CK-MB present, *i.e.*, a CK-MB of 5% is quite different if the total CK activity is 1000 IU/l versus 100 IU/l. Second, the amount of CK-MB detected in the serum directly correlates with the amount of myocardial necrosis.²⁸ Finally, CK-MB fractions exceeding 5% of total CK activity have been documented in postoperative patients who did not experience myocardial infarction.¹⁶

The orthopedic literature contains few studies dealing with serum enzyme elevations in the postoperative period. Berglund and Bergstrom² found elevations of total CK and LD after hip surgery but did not study their isoenzymes.² Galen⁹ performed CK and LD determinations in nine patients treated with total hip arthroplasty and found elevations of total CK and LD, but isoenzyme analysis revealed that these elevations were due to skeletal muscle injury. Healey *et al.*¹⁶ demonstrated that CK-MB comprised 3%–8% of skeletal muscle CK activity when assaying paraspinal muscle biopsies for total CK and CK-MB activity. That study also demonstrated that 37% of patients treated with posterior spinal fusions had false positive elevations of CK-MB exceeding 5% of total CK activity. One patient in that study had a CK-MB absolute value of 369 IU/l ($4100 \text{ IU} \times 9\% \text{ CK-MB}$), but did not experience myocardial infarction.¹⁶

Skeletal muscle injury invariably occurs during total joint arthroplasty of the hip or knee from the necessary dissection and retraction. Consequently, it is easy to explain the elevations of LD-5 and CK-MM, which are the skeletal muscle isoenzymes of LD and CK, respectively. The present data indicate that greater than 95% of total serum CK elevation is due to CK-MM elevation; however, the absolute value of CK-MB did rise significantly following total joint arthroplasty of the hip or knee. These findings support the observation of Healey *et al.*¹⁶ that skeletal muscle contains small but significant amounts of CK-MB activity and that injury

to skeletal muscle can result in significant elevation of serum CK-MB. The maximal elevation of 52 IU/l of CK-MB occurred in a patient who did not manifest any other signs or symptoms suggestive of myocardial ischemia. It is also important to note that the percentages of CK-MM, CK-MB, and CK-BB did not change significantly. Similarly, LD-1:LD-2 did not rise significantly following total joint arthroplasty of the hip or knee.

The maximal rise in total serum CK was seven-fold following total hip arthroplasty and three-fold following total knee arthroplasty, while the rise in total LD was less than two-fold. Since CK-MM accounts for greater than 95% of total CK activity in muscle and LD-5 accounts for only 11% of total activity in muscle, it is apparent that skeletal muscle injury is reflected in total CK activity more so than total LD activity.⁹ Total hip arthroplasty resulted in significantly higher elevations of total CK than total knee arthroplasty (Fig. 4). The increased skeletal muscle dissection and retraction that occur during total hip arthroplasty compared to total knee arthroplasty probably account for this difference.¹⁸

It has been well documented that a circadian periodicity exists regarding the onset of symptoms or first elevations of CK-MB in nonsurgical patients who experience acute myocardial infarction.²⁵ The primary peak incidence of acute myocardial infarction occurs between 4 AM and 12 noon with a secondary peak incidence at 8 PM. This study, therefore, can be criticized for not determining serum enzyme values during the secondary peak incidence if the circadian periodicity applies to postoperative myocardial infarction. It would be expected, however, that the next morning's enzyme determinations (approximately ten hours later) would reveal elevations of serum CK-MB if myocardial infarction occurred during the secondary peak incidence. It is important to point out that all of the present postoperative

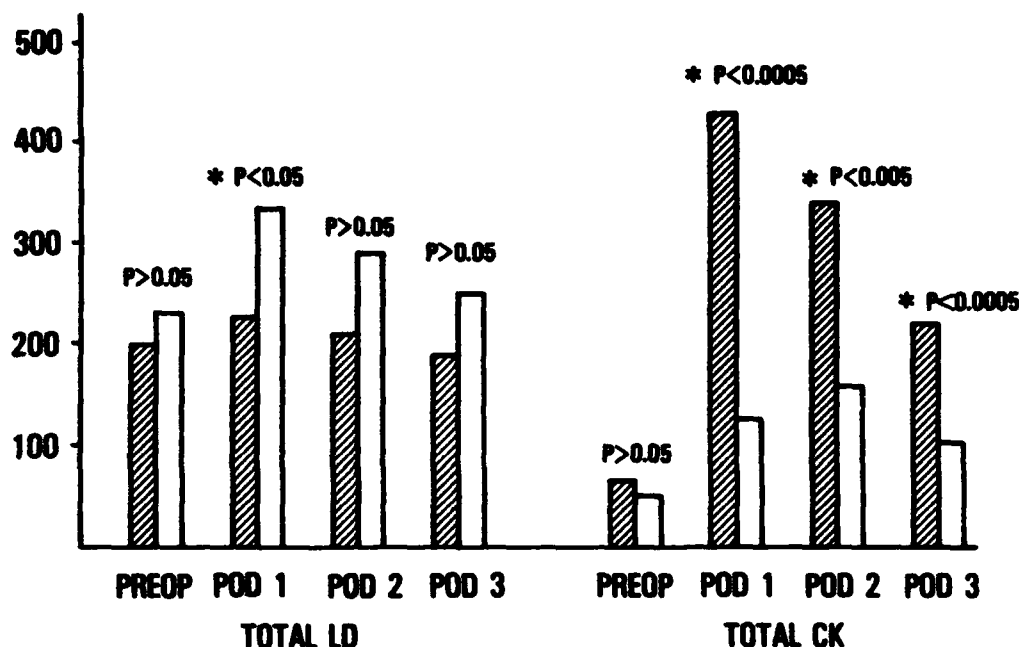


FIG. 4. A comparison of total CK and LD elevations between total hip arthroplasty (shaded area) and total knee arthroplasty (clear area).

enzyme values were obtained from patients during the primary peak incidence of myocardial infarction.

In summary, 45% of the patients in this study were at increased risk for perioperative myocardial infarction based on their age alone, *i.e.*, patients older than 70 years of age. These patients are representative of typical patients who are treated with total joint arthroplasty of the hip or knee.^{1,13} It is important, therefore, to define what effect the trauma of surgery has on these serum markers of myocardial injury if they are to be used in evaluating suspected postoperative myocardial infarction. Total joint arthroplasty of the hip or knee can result in significant elevations of serum CK-MB in patients who have not experienced postoperative myocardial infarction. The percentage of CK isoenzymes and LD-1:LD-2 do not rise significantly following total joint arthroplasty of the hip or knee. Detection of CK-MB in the serum following total joint arthroplasty

of the hip or knee, therefore, is not diagnostic of myocardial injury. Elevations of serum CK-MB exceeding 50 IU/l or 5% of total CK activity combined with LD-1:LD-2 greater than 1.0 should not be attributed to skeletal muscle injury alone.

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