12. MYOGLOBINURIA AND ACUTE RENAL FAILURE

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1 Rhabdomyolysis and Myoglobinuria

Rhabdomyolysis is muscle cell lysis (as hemolysis is lysis of red blood cells) with liberation of cell content into the circulation. As hemolysis liberates hemoglobin, rhabdomyolysis liberates myoglobin. The occurrence of myoglobinuria indicates extensive destruction of striated muscle, that is, the damage of at least 200 grams of normal muscles [1]. That is why myoglobinuria is not prominent after myocardial infarction.

The occurrence of rhabdomyolysis has been supposed to be a rare phenomenon. This is not so. It is a frequent clinical event, but many times it is not recognized because muscular symptoms are slight or absent and/or urine containing myoglobin is so diluted that its color is not different from normal concentrated urine [2]. Furthermore, urinary excretion of myoglobin may be minimal by the time patients reach the hospital. Thus, it may come about that rhabdomyolysis-induced ARF is regarded as ATN of undetermined etiology or even as ARF secondary to glomerulonephritis or to acute interstitial nephritis occurring as a hypersensitivity reaction to antibiotics. Sometimes the condition is recognized by the incidental discovery of elevated serum levels of muscle enzymes. The inconstancy of myoglobinuria in patients with rhabdomyolysis suggests the use of “rhabdomyolysis” rather than “myoglobinuria” to define the syndrome that follows muscle injury.

2 Consequences of Muscle Damage

Rhabdomyolysis allows escape of cell contents into the extracellular fluid: myoglobin; enzymes such as creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (GOT), lactic dehydrogenase (LDH), aldolase; electrolytes such as potassium and phosphate; nucleoproteins and their metabolites and unidentified organic acid(s) [3].

2.1 MYOGLOBIN

Myoglobin is a heme pigment composed of a folded polypeptide (protein) portion, globin, and a prosthetic group, heme, which contains an atom of iron. It is a muscle protein (mol wt 17,800 daltons) that is located in the soluble phase of the sarcoplasma of striated skeletal and cardiac muscles, near the sarcolemma but not bound to it [4, 5]. It is synthesized by muscle ribosomes [6]. Myoglobin normally constitutes 1 to 2% of the wet weight of skeletal muscle, but it may reach 3.5% of the wet weight in highly trained subjects [7].

Only 0.3 mg of myoglobin is released daily from muscles under normal conditions [8]. Normal serum concentrations of myoglobin average 33 ng/ml [9] and do not normally exceed 50 ng/ml [8, 10]. In patients with CRF (serum creatinine greater than 265 μmol/l, 3 mg/dl), serum myoglobin levels have been reported to average 466 ng/ml [9]. In uremic patients on maintenance hemodialysis, mean values of 170 ng/ml [8] and 343 ng/ml [9] have been reported.

For a long time, myoglobin has been regarded as a store for oxygen; it seems, however, that it plays a key role in the transport of oxygen into and within muscle cells through...
its property of reversibly binding molecular oxygen [2, 11]. The weakness that follows myoglobinuria may therefore be accounted for, at least in part, by the loss of this function [2].

Myoglobin is liberated into the bloodstream by any illness that results in rhabdomyolysis, as hemoglobin is liberated by hemolysis. But while hemolysis is followed by a pink, red, or brownish staining of serum, rhabdomyolysis does not stain the serum. The serum is not stained because hemoglobin is bound to a specific serum protein, haptoglobin, and is excreted into the urine only when the binding haptoglobin is saturated; this occurs when hemoglobin concentration exceeds 100 mg/dl [7]. Thus, when hemolysis is mild, the serum is pink while the urine retains its clear yellow color; when hemolysis is massive, both serum and urine are stained. Following rhabdomyolysis, the myoglobin released from muscle cells is readily filtered and appears in the urine (its clearance is 75% that of creatinine). According to Kagen [11] this occurs despite a myoglobin-binding capacity by human serum (apparently due to either an alpha-2 or a beta globulin) of 23 mg/dl; but at serum levels below this maximum-binding capacity, free and bound myoglobin coexist, so that free myoglobin is readily filtered. Thus, stained urine with unstained serum argues in favor of rhabdomyolysis [7]. In order to detect a high value of serum myoglobin (a serum concentration of 5.6 mg/dl has been reported in rhabdomyolysis-induced ARF) [10], blood samples should be obtained soon after the muscle damage since both urinary excretion of the pigment and its metabolism to bilirubin will normalize serum levels within one to six hours [3]. Quantitative myoglobin assays are usually not suitable for clinical use so that serum myoglobin cannot be measured in clinical practice. As we will discuss later in this chapter, however, serum concentrations of enzymes will readily allow the diagnosis of rhabdomyolysis. On the other hand, it has been demonstrated that serum myoglobin levels can be predicted from serum concentrations of creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (GOT), or lactic dehydrogenase (LDH) [12].

It has been stated that the renal threshold for myoglobin is as low as 0.3 mg/dl of plasma [2]; according to others, it is as high as 10 mg/dl [13]. The latter value is too high. Apparently, the correct renal threshold is 0.5 to 1.5 mg/dl [3, 11, 12].

Because of the rapid clearance of myoglobin from plasma, serum levels may be normal by the time the patient is hospitalized; on the other hand, the urine appears grossly stained when its myoglobin concentration is greater than 100 mg/dl [3, 7]. When hospitalization occurs a long time after muscle damage, myoglobinuria may not be detected even by orthotolidine dipstick [3] (a method as sensitive as immunodiffusion or immunoelectrophoresis in detecting myoglobin in urine) [7, 14]. In a recent series of 87 episodes of rhabdomyolysis in 77 patients, a negative orthotolidine dipstick test for myoglobin was found in 26% of patients [3].

2.2 CREATINE PHOSPHOKINASE (CPK)
Creatine phosphokinase (CPK) is an enzyme that transfers a high-energy phosphate moiety from phosphocreatine to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP). Thus, it catalyzes, in striated and cardiac muscles, the following reaction

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\text{ADP} + \text{phosphocreatine} \xrightleftharpoons{\text{CPK}} \text{ATP} + \text{creatine}. 
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This reaction is very important for the continuous chemical regeneration of ATP, which is the immediate energy source for muscular contraction and probably also for sarcolemma integrity [2].

Actually, three isoenzymes of CPK have been identified: CPK–BB (brain type, or CPK–I), CPK–MB (intermediate type, or CPK–II), and CPK–MM (muscle type, or CPK–III) [15]. CPK–I and CPK–II are not present in serum; the isoenzyme CPK–MM, which is normally present in serum (normal values up to 125 mU·ml), is responsible for the normal muscle metabolism [16].

Serum CPK (isoenzyme CPK–MM) is increased in conditions of muscle damage. Elevated levels (233.6 mU/ml) have been observed in uremic patients on maintenance hemodi-