


Morphologic Evidence for Coronary Artery Spasm in Eclampsia

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SUMMARY  Vascular spasm has been considered to be an important component of the eclamptic state. If this abnormal vascular reactivity affects the coronary arteries in eclampsia, one might expect to find areas of myocardial contraction band necrosis, a lesion secondary to coronary reflow after periods of no flow. We reviewed the cardiac findings in the 34 patients with fatal eclampsia (hypertension, edema, proteinuria, and convulsions without evident cause) autopsied at The Johns Hopkins Hospital since 1899, and compared each with the next pregnant or puerperal nontoxicemic autopsied patient. The eclamptic patients were 15–45 years old (average 27 years). Convulsions began antepartum in 21 patients, intrapartum in eight, and postpartum in five. The hearts weighed 200–407 g (average 312 g). One heart had rheumatic valvular disease and one had myocarditis. Histologic study of heart sections showed the presence of contraction band necrosis in 12 cases (35%). The control cases included two patients with rheumatic valvular disease, two with endocarditis, two with myocarditis, two with pericarditis, and one with leukemic infiltration. Only one control patient (3%) had contraction band necrosis (\(p < 0.001\)). The frequent occurrence of myocardial contraction band necrosis suggests that coronary artery spasm may be common in patients who die with eclampsia.

ECLAMPSIA is a disorder unique to pregnancy and the puerperium and is characterized by hypertension, proteinuria, edema and tonic-clonic seizures with loss of consciousness. Although the cause of eclampsia is unknown, vascular spasm plays a major role in its presentation and has been directly observed in the nail beds, bulbar conjunctivae and ocular fundi.1,2 Histologic findings in the kidney and brain from autopsied patients have been attributed, at least in part, to vasospasm.3-6 Although myocardial infarction is unusual in eclampsia, symptoms of congestive heart failure, cyanosis, and postseizure hypotension are frequent, especially in fatal cases.6,7 Most pathologic studies of patients with eclampsia in which the heart has been evaluated, however, were published before 1964 and primarily described regions of myocardial hemorrhage with occasional degenerative changes and focal necrosis.8,9,10,11

In 1964, Sommers and Jennings reported the presence of transverse eosinophilic contraction bands in the posterior papillary muscle of dog hearts after experimentally-induced ischemia and reperfusion.12 Contraction band necrosis, which occurs with a variety of insults to the heart,14 is also the morphologic manifestation of a period of myocardial ischemia followed by reperfusion.16-17 In patients without evidence of fixed coronary artery obstruction or other cause of nonperfusion followed by reperfusion, the finding of contraction band necrosis has suggested the presence of coronary artery vasospasm.18,19 If contraction band necrosis is the result of coronary artery vasospasm, patients who die in the course of a generalized vasospastic disorder might be expected to have myocardial contraction band necrosis. The purpose of this investigation was to determine if patients with eclampsia have an increased incidence of contraction band necrosis in their hearts.

Materials and Methods

We reviewed the cardiac findings in the 34 patients with fatal eclampsia who were autopsied at The Johns Hopkins Hospital between 1899 and 1979. Twenty-seven patients were studied before 1930, the approxi-
mate date when magnesium sulfate came into general use to treat eclampsia. Eclampsia was defined as hypertension (systolic 140 mm Hg or more, diastolic 90 mm Hg or more, or an increase of 15 mm Hg over the usual diastolic pressure), proteinuria (1 g/l or more in a random sample), edema (as evaluated by the obstetrician), and one or more convulsions. Patients were assigned to antepartum, intrapartum, or postpartum eclampsia groups depending upon the time of onset of the first seizure. All postpartum eclamptic patients experienced their first seizure within 6 days after delivery. Patients with hypertension, edema, proteinuria and seizures who were subsequently found to have severe chronic renal failure or renal failure with some other cause for seizure (e.g., meningitis or brain tumor) were excluded from the study. The autopsy records and all histologic sections of heart were reviewed with special emphasis on the presence of contraction band necrosis, coagulation necrosis, coronary artery atherosclerosis, fibrin thrombi, hemorrhage, inflammation, valvular disease and heart weight. Each patient was compared with the next autopsied pregnant or puerperal noneclamptic patient listed in the autopsy files. Means, standard deviations, paired t tests (eclampsia vs controls), and chi-square contingency tests were calculated for quantitative, semiquantitative, and presence/absence variables of interest. All calculations were performed using the Statistical Analysis System (SAS) of computer programs on the IBM 370/3031 in the Information Systems Department of The Johns Hopkins Medical Institutions.\textsuperscript{30}

### Results

The eclamptic patients were 15–45 years old (average 27 years), and the control subjects were 15–45 years old (average 28 years). Convulsions in the eclamptic patients began antepartum in 21 patients (62%), intrapartum in eight (24%), and postpartum in five (14%). Seven were primigravida and 12 were multigravida; the status was unknown in 15. The usual complications of eclampsia were the commonest cause of death. In 25 patients, convulsions led to coma and death; two patients developed postconvulsion pneumonia. Two patients died of a ruptured uterus, one had a ruptured bladder, and one patient had placenta previa. In three patients the cause of death was unclear. Hearts from the eclamptic patients weighed 200–407 g (average 312 g), while hearts in the control group weighed 195–600 g (average 295 g) (table 1). One heart from the eclamptic group had rheumatic valvular disease and another had nonspecific acute myocarditis. The coronary arteries had mild atherosclerosis in seven patients. The control cases included two patients with rheumatic valvular disease, two with endocarditis, two with myocarditis, two with pericarditis and one with lymphocytic leukemic infiltration. Four hearts had mild coronary artery atherosclerosis.

Histologic evaluation of the heart sections showed the presence of contraction band necrosis (fig. 1) in 12 of the eclamptic patients (35%) and in only one of the controls (3%) ($p < 0.001$). When present, contraction band necrosis was usually distributed subendocardially; however, focal midmyocardial and subepicardial necrosis was present in three cases. We could not assess the regional distribution of injury adequately, because the majority of the histologic sections were from the region of the obtuse margin of the left ventricle.

Among the eclamptic patients with contraction band necrosis, two had mild coronary artery atherosclerosis and the remainder had normal coronary arteries at autopsy. Fibrin thrombi in intramyocardial vessels were not found in either group. There was no evidence of remote myocardial infarction in either group of patients, nor was there any correlation between the presence of contraction band necrosis and the time of onset of seizures. Clinical records were incomplete for most patients; however, review of available records failed to document a history of chest pain or electrocardiographic abnormality.

### Discussion

We have reviewed 34 patients who died and were autopsied during or shortly after the onset of eclampsia, and compared them with 34 pregnant noneclamptic controls. The extent of myocardial injury was evaluated semiquantitatively and the clinical records and autopsy findings were reviewed, with special reference to the presence of contraction band myocardial necrosis and clinical heart failure. The frequency of contraction band necrosis in patients with eclampsia was significantly increased.

Eclampsia, an acute disorder of pregnancy and the immediate puerperium, is characterized by hypertension, proteinuria or edema or both after the twentieth week of gestation (preeclampsia) and tonic, clonic seizures without another underlying cause. Eclampsia is often designated as being antepartum, intrapartum or postpartum, depending on when the convulsions appear. The clinical features include epigastric pain, apprehension, excitability, fever, hyperreflexia, headache and convulsions. Well-recognized complications of eclampsia include cerebrovascular accidents, pulmonary edema, cyanosis, uterine tears or rupture, and pneumonia developing during post-seizure coma. Although the cause of eclampsia is un-

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<th>Table 1. Cardiac Pathology</th>
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<tr>
<td><strong>Eclampsia</strong></td>
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<td>(n = 34)</td>
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<tr>
<td><strong>Average heart weight (g)</strong></td>
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<tr>
<td><strong>Contraction band necrosis</strong></td>
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<tr>
<td><strong>Rheumatic heart disease</strong></td>
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<td><strong>Myocarditis</strong></td>
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*By chi-square or t test.*
known, generalized vasospasm is recognized as an important part of its pathophysiology. Retinal arteriolar constriction is an early change in preeclampsia, and increasing blood pressure has been correlated with spasms and tonic constrictions of the retinal arterioles. The vascular constriction may be responsible for hypertension and for focal hypoxia in other organs as well.

With improved clinical recognition and effective early treatment of preeclampsia, true eclampsia is now unusual clinically, and fatal eclampsia is exceedingly rare. In severe cases, however, clinical evidence of cardiac failure, including cyanosis and pulmonary edema, may be marked. Szekely and Snaith for example, noted clinical or electrocardiographic evidence of cardiac abnormalities in seven of 19 patients (37%) with "toxemia." Govan reported cardiorespiratory failure as the cause of death in 47 of 116 cases (43%) of fatal eclampsia before 1961, although autopsies were not performed on all patients.

**Figure 1.** (A) Contraction band necrosis in the myocardium of a patient with fatal eclampsia. The muscle cells have irregular transverse eosinophilic clumps of contractile material in the sarcoplasm. Hematoxylin and eosin; magnification × 900. (B) Focus of myocardial contraction band necrosis. Hematoxylin and eosin; magnification × 300.
Most pathologic studies of patients who died of eclampsia were done before 1960, and although specific lesions in the kidney and liver have been described, cardiac abnormalities have not been well characterized. In an early autopsy study, Schmorl\(^6\) reported the presence of degenerative lesions of the myocardium in 43 of 73 autopsied eclamptic patients, and McKay and co-workers\(^7\) noted petechial hemorrhages and areas of focal necrosis in 40–60% of cases. Way\(^8\) noted myocarditis in two of 33 autopsied eclamptic patients and myocardial hemorrhage in 12, four of whom also had areas of focal necrosis. Acosta-Sison\(^9\) noted primarily fatty or degenerative changes and petechial hemorrhages in an autopsy study of 38 patients, while Bell\(^10\) noted no pathologic evidence of cardiac abnormality in 10 autopsied patients with toxemia. Other authors have noted only the presence of subendocardial or myocardial hemorrhage.\(^11\)

In 1964, Sommers and Jennings\(^12\) reported the presence of irregular, deeply eosinophilic, transverse contraction bands in canine posterior papillary muscle after temporary occlusion of the circumflex coronary artery with reperfusion. Additional studies have shown that while permanent coronary artery occlusion results in irreversible cell injury without net changes in water or electrolytes and leads to well-recognized coagulative necrosis, reperfusion of ischemic myocardium results in striking increases in tissue sodium, chloride, calcium, and water, and decreases in potassium along with disruption of the regular myofibrillar pattern, separation of myofibrils and the presence of prominent contraction bands.\(^13\) Electron microscopy has shown disruption of sarclemma, disorganization of mitochondria, and the appearance of large, dense, intramitochondrial granules along with contraction bands.\(^14\) Kloner and co-workers suggested that the rapid morphologic changes that occur with reperfusion imply an irreversible effect in volume regulation, which is manifested morphologically only if blood flow is restored to the affected cells.\(^15\) Contraction band necrosis has therefore become recognized as a reperfusion patency, and has been observed in patients after cardiac surgery with cardiopulmonary bypass,\(^16\) in patients with papillary muscle rupture and myocardial infarction\(^17\) and in patients with progressive systemic sclerosis.\(^18\) Several recent articles have reviewed the importance of coronary artery spasm in Prinzmetal's angina, in angina experienced by munitions workers chronically exposed to nitroglycerin when withdrawn from their environment, and as a complication of coronary artery catheterization.\(^19\) It is therefore likely that coronary artery spasm can, in certain cases, result in angina and even myocardial infarction.\(^20\)

We thought that the current understanding of the significance of contraction band necrosis justified a reevaluation of the myocardial pathology in patients who died during or shortly after eclamptic convulsions. We found much more myocardial contraction band necrosis in patients who died with eclampsia than in controls, which suggests the potential of more significant myocardial damage in eclampsia than previously recognized. Further study of patients with eclampsia or other disorders manifested by generalized vasospasm may provide additional information concerning the cause and significance of contraction band necrosis itself.

References

23. Herdson PB, Sommers HM, Jennings RB: A comparative
Determinants of Arrhythmic Death Due to Coronary Spasm: Effect of Preexisting Coronary Artery Stenosis on the Incidence of Reperfusion Arrhythmia

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SUMMARY Coronary spasm can occur in the presence or absence of coronary artery disease. We therefore determined the effect of preexisting coronary stenosis on the incidence of ventricular fibrillation during reperfusion after circumflex coronary artery (CFX) occlusion. Twenty dogs underwent a 30-minute open-chest CFX occlusion. During reperfusion, CFX blood flow was restricted by a partial occluder. In dogs that survived reperfusion, peak CFX flow was 91 ± 44% of baseline (mean ± SD) compared with 163 ± 68% in dogs that died of ventricular fibrillation (p < 0.02). In another 17 dogs, the left anterior descending coronary artery was gradually occluded by an ameroid constrictor. After 17–39 days, the CFX was acutely occluded for 30 minutes and then reperfused. Collateral flow to the CFX, measured by microspheres, was 27.6 ± 28.3 ml/min/100 g−1 in dogs that died of reperfusion ventricular fibrillation, compared with 64.4 ± 27.2 ml/min/100 g−1 in surviving dogs (p < 0.02). Thus, the risk of reperfusion ventricular fibrillation is greater in dogs with normal coronary arteries than in dogs with a flow-limiting partial stenosis of the artery undergoing transient occlusion, or chronic stenosis of a second coronary artery inducing collateralization to the artery subsequently undergoing transient occlusion. These results suggest that the risk of ventricular fibrillation during release of coronary spasm may be greater in patients without than in those with coronary artery disease.

ACUTE OCCLUSION of a previously patent coronary artery is a major cause of sudden death in coronary artery disease. However, ventricular fibrillation (VF) due to reopening of a transiently occluded coronary artery and subsequent reperfusion of ischemic myocardium may also be responsible for sudden death in patients with coronary artery disease. Reperfusion VF could result from lysis of platelet plugs or thrombi, or from release of coronary artery spasm. Angiographic studies have revealed that spasm occurs in both apparently normal and partially stenosed coronary arteries.

Most animal models of reperfusion, however, are analogous only to release of occlusion in normal arteries. That is, the return of blood flow to the ischemic myocardium is unrestricted. If, however, transient occlusion occurs in an artery already partially stenosed by atherosclerotic disease, the level of blood flow during reperfusion would be reduced by the pre-existing stenosis. This situation would be better modeled by coronary artery occlusion followed by partial reperfusion. The incidence of reperfusion VF under such conditions is unknown; nor has the effect of chronic coronary occlusion of arteries other than the one undergoing transient occlusion been studied in relation to the outcome of reperfusion.

Therefore, to determine the effect of preexisting coronary stenosis on arrhythmias during reperfusion, we investigated the incidence of VF during sudden but restricted reperfusion of the circumflex coronary artery (CFX) and during sudden unrestricted reperfusion of the CFX, but in the setting of various degrees of collateral flow stimulated by prior gradual occlusion of the left anterior descending coronary artery (LAD).

Materials and Methods

Foxhounds of either sex that weighed 17–34 kg, ranging in age from 8 months to 4 years, were studied.

Experimental Protocol

Restricted Reperfusion

The dogs were anesthetized with i.v. sodium pentobarbital; the initial dose was 26.5 mg/kg and additional doses (5 mg/kg) were given as needed. The dogs

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