



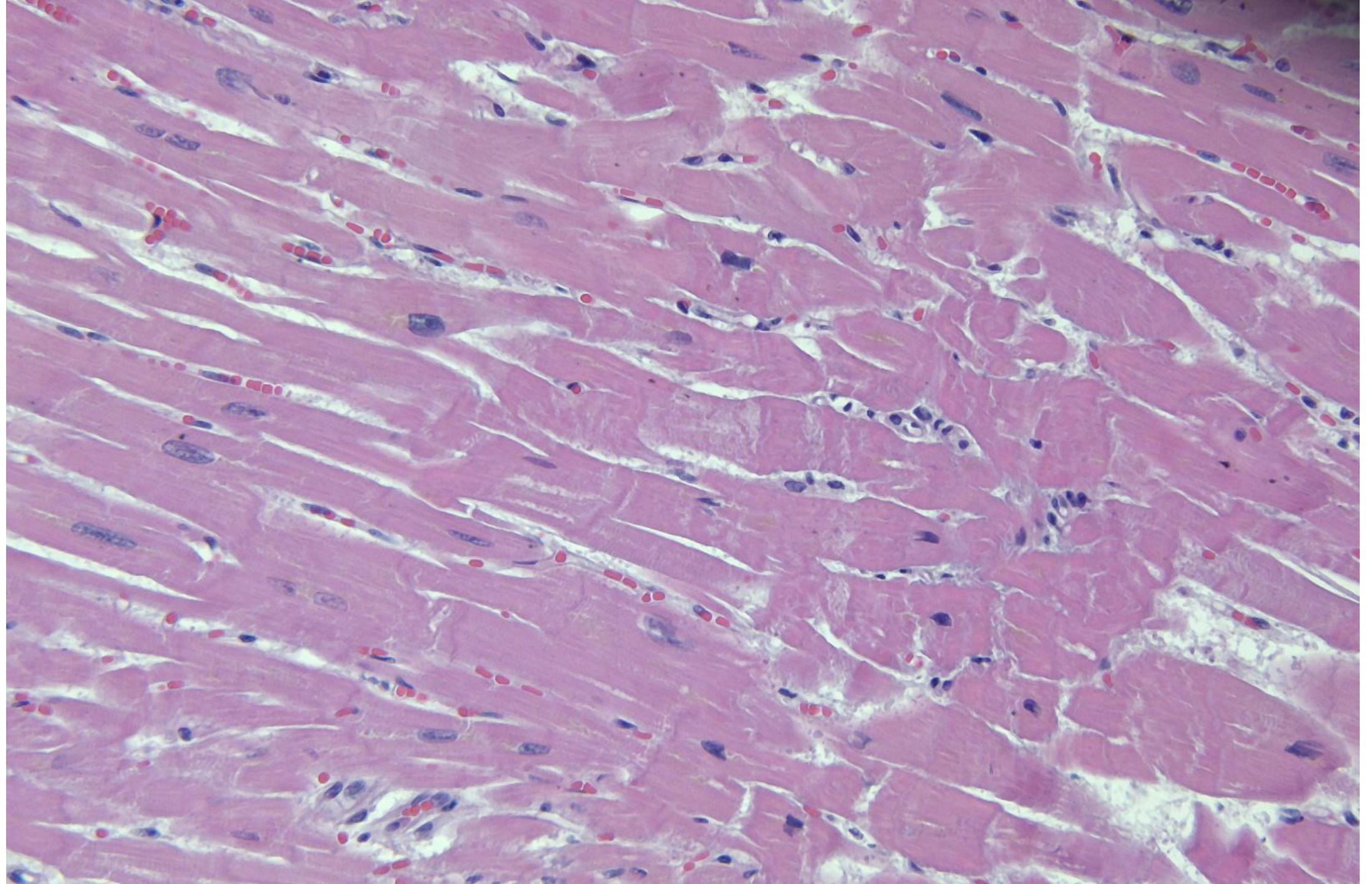
Case #76

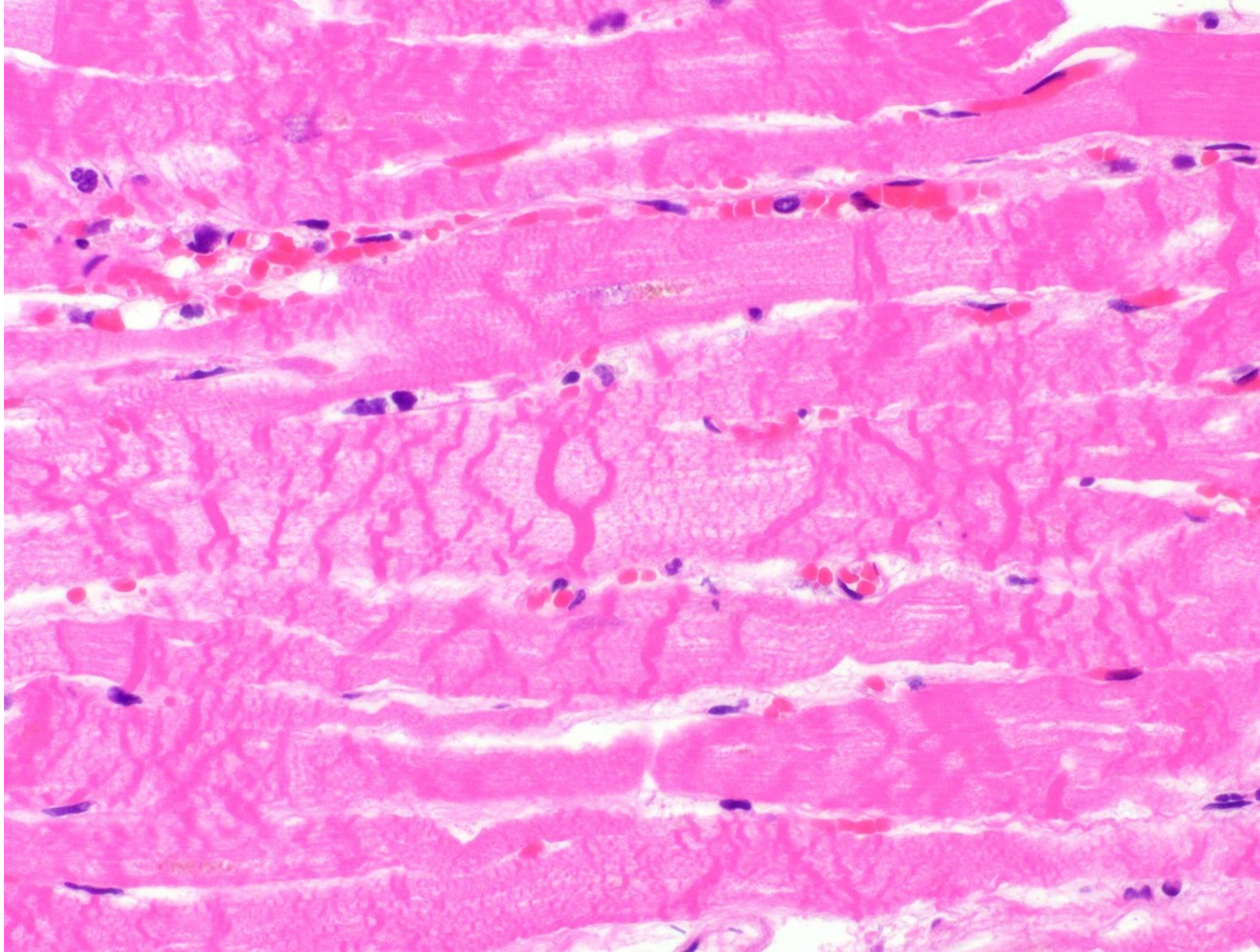
NAME Educational Activities Committee

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1. A 52-year-old man had been feeling “unwell” with fatigue, diarrhea, and abdominal pain for an unknown period of time. He was eventually transported to the hospital and died 24 hours later. The histologic features seen in the left ventricle are most commonly associated with which of the following drugs?

- Epinephrine
- Methylene blue
- Hydroxychloroquine
- Doxorubicin
- Tafamidis

Answer...

A. Epinephrine (CORRECT ANSWER, 55.27% of responses)

The patient had an atypical presentation of ischemic cardiac disease. The histology images depict contraction band necrosis, which is an early response to myocardial ischemia. This damage typically arises a few hours after the insult. Epinephrine is a common medication used in cardiopulmonary resuscitation to correct arrhythmias and is known to cause coronary vasospasm which can lead to myocardial ischemia. Contraction band necrosis can therefore be seen following prolonged cardiopulmonary resuscitation.

In this case, the decedent underwent aggressive CPR with multiple doses of epinephrine. It should be noted that contraction bands are very non-specific, resulting from anything that could cause ischemia including atherosclerosis, hypertension with cardiac hypertrophy, resuscitation, sepsis, and drug use (cocaine, methamphetamine).

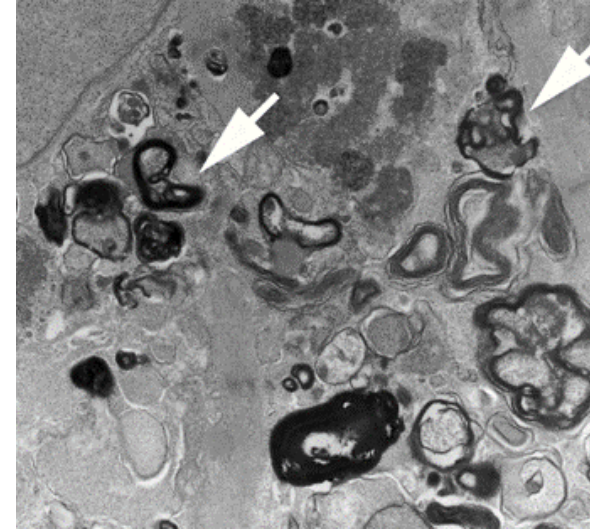
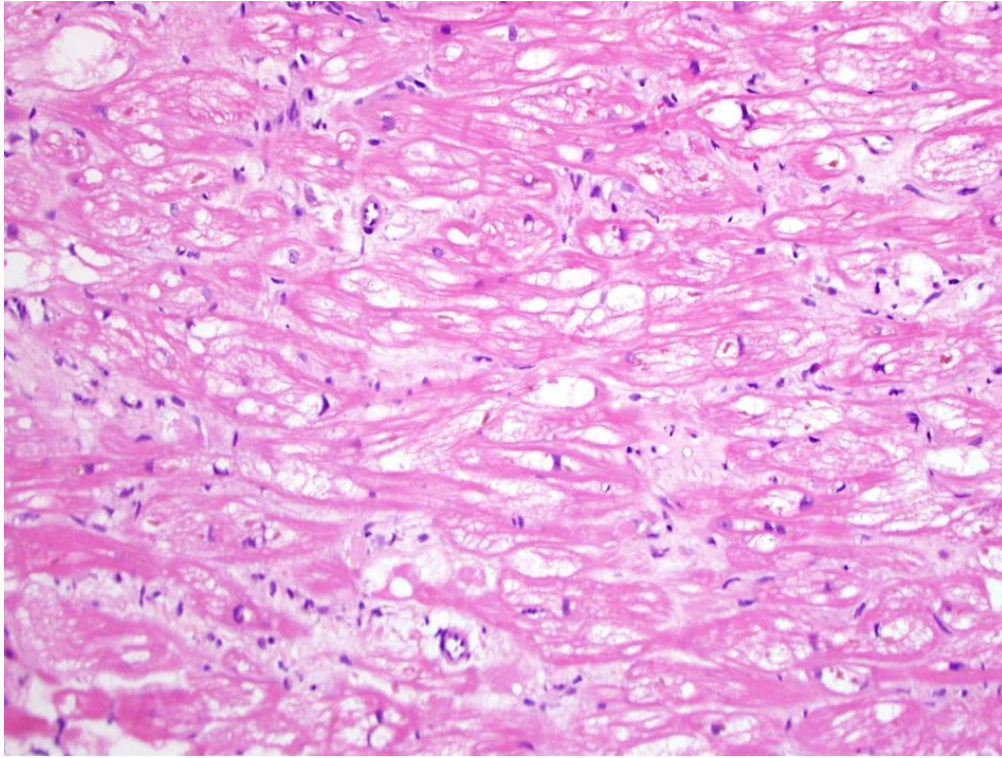
Other responses:



B. Methylene blue (3.63% responses)

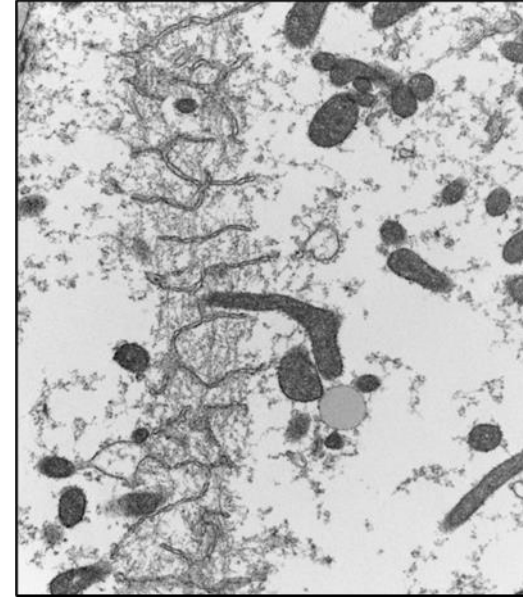
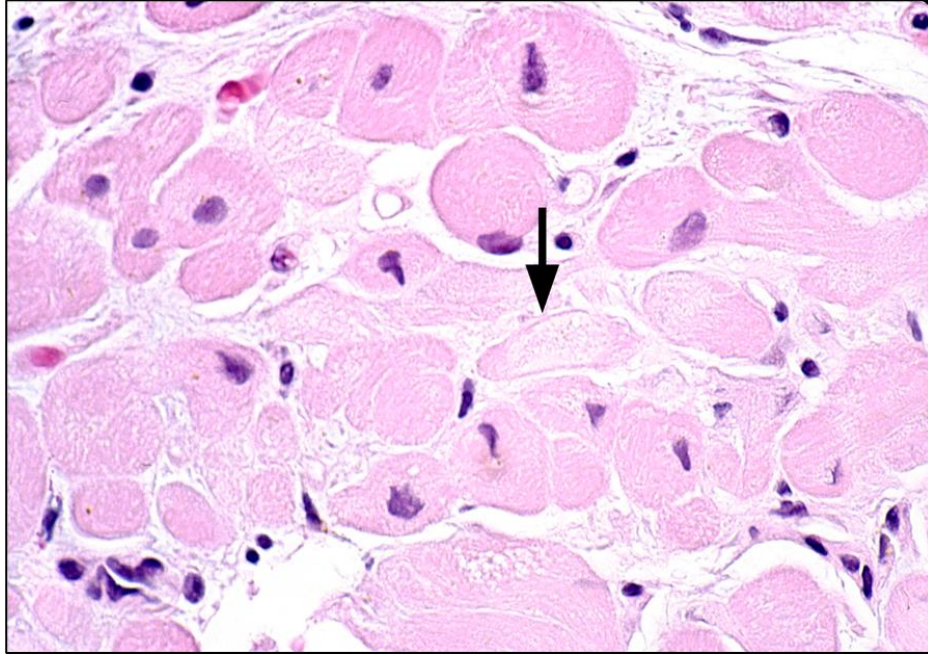
Methylene blue is traditionally used to treat methemoglobinemia due to its ability to accelerate the reduction of ferric (Fe^{3+}) iron to ferrous (Fe^{2+}) iron. However, it's been increasingly utilized in the treatment of refractory shock, wherein it is thought that loss of vascular tone is (at least partially) attributable to nitric oxide release. Methylene blue inhibits the nitric oxide-cyclic guanosine monophosphate pathway (i.e., interferes with NO production) leading to increased systemic arterial pressure.

Interestingly, the drug is metabolized *in vivo* into a colorless leukomethylene blue. However, when that substance is then again exposed to atmospheric oxygen at autopsy, auto-oxidation leads to regeneration of the blue drug and (dis)coloration of the tissues.



C. Hydroxychloroquine (15.72% responses)

Upon ultrastructural examination, hydroxychloroquine toxicity has electron-dense structures called myeloid figures (arrows) as well as curvilinear bodies. Mechanistically, the medication is lysosomotropic, leading to increased pH within the lysosome and subsequent inhibition of enzymes within this organelle. As such, metabolic products accumulate in the cytosol, leading to the characteristic ultrastructural findings.



EM image with myofibrillar loss and organelle degeneration

D. Doxorubicin (22.63% responses)

Doxorubicin is used to treat solid tumors by inhibiting topoisomerase II to cause death of cancer cells. Cardiotoxicity is a known side effect, and it can cause irreversible damage to the heart. One mechanism is the generation of reactive oxygen species, leading to apoptosis of the myocytes. Since myocardial ischemia is not caused by doxorubicin, it would not be seen in these cases. Light microscopy shows edema, fibrosis and myocyte vacuolization. Electron microscopy shows myofibrillar loss and organelle degeneration.

E. Tafamidis (2.76% responses)

Tafamidis is used for the treatment of amyloidosis. Amyloidosis is caused by misfolded transthyretin proteins, which then become deposited in the extracellular space of the tissues. This drug stabilizes transthyretin protein, reducing disease progression and mortality. While amyloidosis is known to cause cardiomyopathy, there are no known adverse cardiac effects of tafamidis.

Reference

- Cheng TO. Contraction band necrosis. *J Clin Pathol*. 1996 Dec;49(12):1022. doi: 10.1136/jcp.49.12.1022-a. PMID: 9038748; PMCID: PMC499660.