Calcium channel blockers (CCBs) have been used since the late 1970s for a variety of cardiovascular indications. They exert their clinical effect by binding to the α_{1C}-subunit on voltage-gated L-type calcium channels thus inhibiting calcium-influx through the ion pore. L-type calcium channels are present on a variety of tissues including myocardium and vascular smooth muscle. The two primary classes of CCBs include dihydropyridines (ie. amlodipine, nifedipine, nimodipine) and nondihydropyridines (verapamil and diltiazem). They differ in their relative selectivity for various tissues at therapeutic doses. Dihydropyridines primarily act as peripheral vasodilators acting on the L-type calcium channels on vascular smooth muscle. Nondihydropyridines have the greatest affinity for the myocardium and inhibit both the sinoatrial and atrioventricular nodes.

CCB toxicity is largely and extension of the clinical effects with the hallmark findings of hypotension and bradycardia. This is a result of depression of myocardial contraction in addition to peripheral vasodilation. Initial management includes fluids and vasoactive medications (norepinephrine is a reasonable choice) for hypotension, atropine for initial bradycardia, and administration of calcium to increase the transmembrane gradients. For patients who are severely poisoned, the therapy of choice is high-dose insulin therapy (HDIT). During CCB toxicity the heart has a greater carbohydrate demand. In response, the liver increases glycogenolysis to make more glucose available. CCBs inhibit insulin release from the pancreas in addition to interfering with glucose transport and phosphatidylinositol 3-kinase glucose transport. The result is the inability for glucose to enter myocardial tissue. HDIT supports the metabolic demands associated with cardiogenic shock and augments calcium processing, thereby increasing myocardial contractility and improving tissue perfusion. Clinical effects can be expected within 15-40 minutes after initiation.

Inotropic effects of insulin had first been recognized in 1927, however its first use in humans occurred in 1999. Yuan and colleagues documented a case series of HDIT in five patients with either isolated or mixed CCB toxicity. Patients were managed with a mean of 0.5 IU/kg/hr (range 0.1-10 IU/kg/hr) for a mean duration of 27 hours (range 9-49 hours). All patients recovered without permanent sequelae. Hypoglycemia as a result of HDIT only occurred in one patient. Hypokalemia occurred in 3 patients; however, this is an expected effect of HDIT due to the intracellular shift of potassium. Overall, the therapy was well tolerated. Since the original case series there have been numerous other case reports and case series of HDIT utilization in CCB toxicity with good overall survival. Although there is potential for reporting bias and confounding factors due to the nature of case report level data, there is a benefit for HDIT that must be acknowledged.

When initiating HDIT, myocardial function should be assessed using bedside ultrasound or another available form of monitoring. With decreased myocardial function, a bolus of regular human insulin should be administered at a dose of 1 unit/kg IV along with a bolus of 0.5 g/kg of IV dextrose if blood glucose is below 300 mg/dL. An insulin regular infusion at a dose of 1 unit/kg/hr should be started immediately following the bolus. It is best to concentrate the insulin infusion to avoid volume overload which may result in pulmonary edema. Insulin is stable in concentrations up to 16 units/mL for up to 14 days. Direct communication should be made to the pharmacy to avoid confusion with insulin concentrations. In addition to the insulin infusion, a dextrose infusion should be initiated at 0.5 g/kg/hr.
Ideally concentrated dextrose solutions such as D20W or D50W should be infused via a central line. D10W can be used peripherally until central access can be obtained if not already done. Insulin may be titrated up by 1 unit/kg/hr increments up to a typical max of 10 units/kg/hr, although there are case reports of up to 22 units/kg/hr being used.\textsuperscript{3}

While on HDIT, glucose should be monitored every 15 to 30 minutes while titrating the dose and then every hour thereafter to maintain glucose levels between 100-200 mg/dL. Hypokalemia is expected due to the intracellular shift of potassium ions. Serum potassium should be monitored every hour while titrating insulin and then every 4 to 6 hours once at a stable dose. Potassium should be only be repleted if serum levels fall below 3 mEq/L to avoid hyperkalemia as low serum levels during HDIT are not reflective of a total body depletion of potassium.\textsuperscript{3} Titrating HDIT off can be accomplished by decreasing the dose by 1 unit/kg/hr every hour with reassessment of myocardial function after each dose change. The dextrose infusion should be continued after discontinuation of HDIT to avoid hypoglycemia. Serum glucose and potassium should continue to be monitored until the insulin is eliminated.\textsuperscript{3}
References: