Primary hemochromatosis and secondary iron-overload conditions, such as thalassemia and sickle cell anemia, result in iron overload and are among the most frequently inherited disorders at an international scale. The prevalence and global clinical burden of iron overload is increasing with epidemic proportions. Iron-overload cardiomyopathy is a common cause of mortality in patients with secondary iron overload and is a major comorbidity in patients with primary hemochromatosis. This cardiomyopathy is characterized by diastolic and systolic dysfunction, biventricular dilatation, and bradyarrhythmias. Although chelation therapy can reduce the iron burden in patients with iron overload, toxicity and expense limits its widespread use in developing and undeveloped countries, where the global burden from iron overload is particularly high. In this issue of the *Canadian Journal of Cardiology*, Khamseekaew et al. reviewed the role of L-type Ca^{2+} channels (LTCCs) and excitation-contraction coupling in iron-induced myocardial injury, and the various levels of experimental data are summarized. The role of Ca^{2+} channels has been clearly highlighted with an emphasis on the LTCC as a major portal for entry of iron into thalassemic murine hearts resulting in iron-overload cardiomyopathy. Khamseekaew et al. also concluded that T-type Ca^{2+} channels (TTCCs) can also mediate iron entry in the heart. However, TTCCs are expressed at low levels in the heart, and the drug used, efonidipine, blocks both LTCCs and TTCCs, thus making the interpretation of studies with these agents difficult.

Specifically, the susceptibility of these tissues to iron-mediated damage remained a mystery for several decades until animal studies showed that LTCCs are critical mediators of iron entry into excitable tissues like cardiomyocytes and pacemaker cells of the heart, as well as excitable cells in other tissues. LTCCs in all cardiomyocytes in the heart are the major regulators of excitation-contraction (EC) coupling in cardiomyocytes. As highlighted by Khamseekaew et al., this is particularly relevant because cardiac EC coupling is very sensitive to oxidative stress, which is elevated in iron-overload cardiomyopathy in association with altered Ca^{2+} cycling and impaired cardiac function. In isolated cardiomyocytes, Fe^{2+} also interferes with the normal Ca^{2+}-mediated inactivation process in LTCCs, resulting in increased Ca^{2+} influx, thereby potentially contributing to the diastolic dysfunction observed during early iron overload. Although these findings are based exclusively on *in vitro* studies, studies in mice have shown that early iron overload is associated with decreased sarcoendoplasmic reticulum Ca^{2+} ATPase2a ventricular levels (and increased Na^{+}/Ca^{2+} exchanger levels), resulting in elevated diastolic [Ca^{2+}]i levels in ventricular cardiomyocytes, whereas more
advanced iron-overload cardiomyopathy is associated with increased myocardial fibrosis.\textsuperscript{19} Iron overload in mice also reduced Ca\textsubscript{v1.3}-dependent L-type Ca\textsuperscript{2+} currents in the SA node cells in association with bradycardia, altered electrical conduction, and atrial fibrillation,\textsuperscript{7} which are also seen in patients with iron overload.\textsuperscript{3}

The observation that iron uptake into the heart (and other excitable tissues) occurs through LTCCs is the basis for the use of LTCC blockers, like amlodipine and verapamil, to reduce iron accumulation in the heart and prevent the associated heart disease in mice with iron overload.\textsuperscript{9} Verapamil treatment has also been shown to reduce cardiac iron levels in hemojuvelin knockout mice, a genetic model of hemochromatosis.\textsuperscript{20} In humans, several case reports have demonstrated that LTCC blockers have had therapeutic effects in patients with secondary iron overload and heart disease.\textsuperscript{21} An early phase I clinical study with amlodipine showed positive results in patients with thalassemia major,\textsuperscript{22} and there are 3 current phase II/III trials (clinicaltrials.gov; NCT02065492) (Karachi, Pakistan), NCT01395199 (São Paulo, Brazil), and NCT02474420 (Toronto, Canada) testing the therapeutic effects of amlodipine in addition to standard therapy in patients with secondary iron overload. The translation of the concept that iron uptake into the heart occurs through L-type Ca\textsuperscript{2+} channels has elucidated a tailored therapy for iron-overload cardiomyopathy based on the fundamental understanding of disease pathogenesis. Clearly amlodipine is likely to provide benefits in iron-overload cardiomyopathy because of the central role of LTCC-mediated Fe\textsuperscript{2+} entry (and oxidative stress) in the pathogenesis of iron-overload cardiomyopathy. Amlodipine represents an ideal calcium channel blocker (CCB) to be used in patients with iron-overload cardiomyopathy because of its ability to provide a delicate balance between blockade of myocardial LTCCs while avoiding excessive SA and AV node blockade, thereby triggering bradyarrhythmias, a well-known complication of iron overload.\textsuperscript{3,25} The beneficial effects of these CCBs could involve alternative mechanisms of action such as improved myocardial microvascular perfusion.\textsuperscript{4,25} Amlodipine also possesses antioxidant properties,\textsuperscript{3} and given the pivotal role of oxidative stress in iron-overload cardiomyopathy,\textsuperscript{14,19,23} amlodipine may have therapeutic benefits independent of the inhibition of cardiac LTCCs. Finally, future work may need to consider how other potential mechanisms for iron transport contribute along with LTCCs to the cardiomyopathy induced by iron overload, such as the divergent metal transporter 1, transferrin receptors, and ferroportin.\textsuperscript{23}

**Funding Sources**

Gavin Y. Oudit and Peter H. Backx are supported by operating grants from the Canadian Institute of Health Research and Heart and Stroke Foundation.

**Disclosures**

The authors have no conflicts of interest to disclose.

**References**


