Ischemic heart disease stands as the foremost global cause of mortality. Myocardial ischemia results in damage to cardiomyocytes which can further lead to impaired heart function. However, the extent of ischemic injury hinges not only on the intensity and duration of the ischemic stimulus but also on cardiac tolerance to ischemia. Therefore, it is extremely important to unravel the molecular basis of cardioprotective interventions such as adaptation to chronic hypoxia or fasting. We focused on the novel epitranscriptomic mechanisms around RNA modifications – N^6-methyladenosine (m^6A) and N^6,2'-O-dimethyladenosine (m^6Am). Our findings revealed that while most epitranscriptomic modifiers displayed differential regulation in the heart following hypoxic adaptation and fasting, demethylases (ALKBH5 and FTO) were consistently upregulated after these cardioprotective interventions. Furthermore, we detected a discernible reduction in cardiac total RNA methylation levels after fasting. On the contrary, transcripts *Nox4* and *Hdac1*, both of which play a role in the cytoprotective action of ketone bodies, exhibited increased methylation in hearts of fasting rats. Finally, inhibition of epitranscriptomic demethylases ALKBH5 and FTO decreased the hypoxic tolerance of adult rat primary cardiomyocytes isolated from fasting rats. Collectively, our findings underscore the intricate regulation of the epitranscriptomic machinery surrounding m^6A and m^6Am modifications in cardioprotective interventions like adaptation to chronic hypoxia and fasting. Therefore, this complex regulation may play an important role in the induction of the cardioprotective phenotype.