Therapeutic hypothermia is a recognized intervention for patients who experience cardiac arrest and can improve neurological function and mortality by protecting against the processes of reperfusion and reoxygenation and reducing the metabolic rate for oxygen. In addition to its favorable effects, hypothermia plays another role in the disease. For example, advanced hypothermic conditions, including disasters or activities in cold places, are believed to induce life-threatening arrhythmia. Recent research has revealed that ventricular arrhythmias (VA) can occur in mild hypothermic conditions, and that they are usually therapy-resistant and life threatening. Pikel, et al. showed that hypothermia could amplify the hypothermia-induced transmural dispersion of repolarization, which was directly dependent on the depth of cooling andrewarming. The number of arrhythmias that occurred during advanced hypothermia is more than that during mild hypothermia. Even during mild hypothermia, arrhythmias such as ventricular tachycardia also occur more frequently than at normal temperature. Saitoh, et al. have addressed this point with porcine heart using systematic protocols. Their study findings indicated mild hypothermia was arrhythmogenic, and that induced arrhythmias are refractory for therapy. Here we will outline the possible mechanism of arrhythmias induced by hypothermia.

Cold-inducible RNA-binding protein (CIRP), which is also called CIRBP or A18 hnRNP, is a type of cold shock protein first identified in mammalian cells, and its expression is increased by cold stress. CIRP is characterized by one amino-terminal RNA recognition motif (RRM) which has been found to have a function of post-transcriptional regulation of gene expression and one carboxyl-terminal arginine-glycine-glycine-rich region (RGG) which may regulate nucleocytoplasmic translocation. Although CIRP is predominantly located in the nucleus, under stress conditions it can migrate to the cytoplasm. Yang, et al. revealed that methylation and phosphorylation of CIRP might be required for CIRP to translocate from the nucleus to cytoplasm.

CIRP can be upregulated by hypothermia or cold stress in different species and then regulates gene transcription and arrests the cell cycle to protect the cells against the decreased temperature. Ultraviolet radiation, mild hypoxia, and glucose deprivation can also increase the expression of CIRP. On the other hand, its expression is decreased by heat stress and inflammatory cytokines such as TNF-α and TGF-β.

Three kinds of CIRP transcripts which have different transcriptional start sites have already been identified. One of the transcripts of CIRP is expressed at 37°C, which has the shortest 5'-UTR and the other two are expressed at 32°C which have larger 5'-UTR. The extent of the expression of CIRP is dependent on the temperature. The lower the temperature is, the more total CIRP is expressed. A recent study has identified its enhancer, which is called the cold-responsive element, that can be combined with transcriptional factor - specificity protein 1 (SP1) in the 5' region of the CIRP gene. Under hypothermia, SP1 will be induced in the nucleus and binds to the cold-responsive element to increase the expression of CIRP.

CIRP positively or negatively regulates gene expressions by post-transcriptional control via binding to the 5'-untranslated regions (UTRs) or 3'-UTRs. The positive (beneficial) effects of hypothermia on the body depend on induced CIRP. Although CIRP plays positive roles in many aspects of diseases like anti-apoptosis and anti-inflammation, some negative (harmful) effects of CIRP have also been reported.

In the heart, it has been established that CIRP can affect cardiac repolarization by suppressing expression of the α-subunits of transient outward potassium current (Ito) channels in cardiomyocytes as negative effects of CIRP in the heart. The Ito can be divided into subunits, including Ito,fast and Ito,slow. The Ito,fast subunit consists of Kv4.2 and Kv4.3 channels which are encoded by KCND2 and KCND3 genes, respectively. Importantly, the subunits KCfIP2 and DPP6 are necessary for Ito,fast. Ito,fast is mainly formed by Kv4.3 and KCfIP2 in most mammalian cells. Additionally, the expression of KCfIP2 in epicardial cells is greater than that in endocardial cells, which produces the Ito gradient across the ventricular wall. Oleisen, et al. showed that Kv4.3 was associated with early-
The mechanism of arrhythmia caused by CIRP. CIRP is induced by hypothermia and can suppress the expression of α-subunits of Ito and KCND2/3.

Figure

In conclusion, hypothermia induced proteins have positive and negative effects on the heart. The greater the temperature decrease, the more negative the effect will be.

Until now, there has been no definite low-temperature point that is good for patients during treatment. More research should be conducted in order to identify the most appropriate low temperature point for therapies in the future.

Disclosures

Conflicts of interest: None.

References