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MYOCARDIAL INFARCTION TREATMENT THROUGH HYPOXIC ENVIRONMENT AND T_3 INHIBITORS: A HYPOTHESIS FROM EXISTING STUDIES

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ЛЕЧЕНИЕ НА МИОКАРДЕН ИНФАРКТ ЧРЕЗ ХИПОКСИЧНА СРЕДА И T_3 ИНХИБИТОРИ: ХИПОТЕЗА ВЪЗ ОСНОВА НА СЪЩЕСТВУВАЩИТЕ ПРОУЧВАНИЯ

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Abstract. Myocardial infarction is one of the leading causes of global mortality and is strongly associated with permanent damage and sudden cardiac death. The human heart loses its proliferative ability after birth as cardiomyocytes are compelled to differentiate into mature cells focusing on hypertrophy. Based on the review of existing studies, we hypothesised that the combination of hypoxia and 3, 3', 5-triiodo-L-thyronine (T_3) inhibitors could potentially be a more sustainable treatment method. We searched trusted scientific databases, such as PubMed, Directory of Open Access Journals (DOAJ), and Scopus, for relevant studies. T_3 is a physiological hormone that was found to promote cardiomyocyte differentiation and inhibit its proliferation. Studies implied that inhibiting T_3 during perinatal development could preserve the heart's proliferative and regenerative capacities for a more extended period. Several animal experiments and human studies have found that inducing a hypoxic environment could revert cardiomyocytes to their endogenous proliferative state. However, long periods of hypoxia were not sustainable due to its deleterious effects on the human body. We suggested that administering T_3 inhibitors after the cardiomyocytes have been reverted under hypoxic conditions could enable patients to leave the hypoxic environment while preventing physiological maturation by T_3, thus preserving the heart's regenerative capacity.

Key words: myocardial infarct; regenerative medicine; hypoxia; T_3 thyroid hormone

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Резюме. Инфарктът на миокарда е една от водещите причини за глобална смъртност и е тясно свързан с трайно увреждане и внезапна сърдечна смърт. Човешкото сърце губи своята пролиферативна способност след раждането, тъй като кардиомиоцитите са принудени да се диференцират в зрели клетки, фокусирани върху хипертрофия. Въз основа на прегледа на съществуващи проучвания, ние предположихме, че комбинацията от хипоксия и инхибитори на 3, 3', 5-трийодотиронин-L-тиронин (T_3) потенциално може да бъде по-устойчив метод на лечение. Търсихме подходящи проучвания в надеждни научни бази данни, като PubMed, Directory of Open Access Journals (DOAJ) и Scopus. T_3 е физиологичен хормон, за който е установено, че насърчава диференциацията на кардиомиоцитите и инхибира тяхната пролиферация. Проучванията предполагат, че инхибирането на T_3 по време на перинаталното развитие може да запази пролиферативния и регенеративен капацитет на сърцето за по-дълъг период. Няколко експеримента с животни и изследвания върху хора са открили, че предизвикването на хипоксична среда може да върне кардиомиоцитите в тяхното ендогенно пролиферативно състояние. Дългите периоди на хипоксия обаче не са били устойчиви поради вредните ù ефекти върху човешкото тяло. Ние предположихме, че прилагането на T_3 инхибитори, след като кардиомиоцитите са били върнати при хипоксични условия, може да позволи на пациентите да напуснат хипоксичната среда, като същевременно предотвратява физиологичното съзряване от T_3, като по този начин запазва регенеративния капацитет на сърцето.

Ключови думи: инфаркт на миокарда; регенеративна медицина; хипоксия; T_3 тиреоиден хормон

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Introduction

The heart is a vital organ in the cardiovascular system. It pumps blood, oxygen, and nutrients crucial to maintaining bodily functions. Any damage to or cessation of the heart will impair the whole human body system [1]. Heart diseases are one of the leading causes of global mortality, especially in developed industrial countries [2]. One of the primary heart diseases is myocardial infarction, which is strongly associated with sudden cardiac death [3, 4]. The prevalence of myocardial infarction reaches 3 million people worldwide and is responsible for more than 1 million deaths annually in the United States alone [5]. Despite its crucial function in the human body, unlike many other organs, the heart does not have the regenerative ability to heal from sustained damage. The human heart loses its proliferative ability after birth as cardiomyocytes are compelled to differentiate into mature cells focusing on hypertrophy. Hence, cardiomyocytes are replaced by fibrosis and scar tissue instead of regenerating when the heart is damaged [6]. These permanent damages to the heart also put it at a higher risk for the occurrence of more severe cardiac complications in the future. Therefore, researchers and clinicians are currently striving to find a sustainable cure for myocardial infarction to improve patient's overall quality of life [7].

Currently, available strategies in cardiomyocyte replacement include transplantation of stem and progenitor cells [8, 9], direct reprogramming of resident cardiac fibroblasts [10], and reactivation of endogenous regenerative mechanisms [11-13]. The first transplantation of progenitor cells for heart regeneration was accomplished by utilising skeletal myoblasts. However, this study yielded no findings because muscle cell progenitors could not develop into cardiac muscle cells [8]. More recent research has concentrated on cardiomyogenic progenitor cells or their differentiated descendants [9]. Another strategy developed for cardiomyocyte replacement is directly reprogramming one somatic cell type into another without entering the pluripotent state. Direct reprogramming of induced cardiomyocytes (iCMs) from fibroblasts has emerged in the recent decade as a viable technique for cardiac regeneration [10].

While two of the previously mentioned strategies strive to discover, amplify, differentiate, and transplant stem and progenitor cells, one alternative approach is the in situ reactivation of endogenous cardiac progenitor cells (CPC) regenerative activity. Recent findings suggest that the adult mammalian heart has an endogenous restoration program mediated by resident CPCs, perhaps through paracrine contribution [11]. Shapiro et al. found that injecting an adenovirus with complementary DNA expressing cyclin A2 into infarcted pig hearts induced cytokinesis in mature cardiomyocytes and reduced fibrosis [12]. Nguyen et al. also discovered that cardiomyocyte-specific deletion of Hoxb13 can prolong the postnatal window of cardiomyocyte proliferation and restart the cardiomyocyte cell cycle in the adult heart [13]. Another novel modality currently being studied and developed is perhaps the next potential breakthrough in reactivating the heart's regenerative ability. It has been postulated that exposure to a hypoxic environment could revert the heart to its regenerative state, thus creating a window period for the heart to repair its damages. However, the limitation of this method is that the human body cannot sustain long periods of hypoxia as it could induce various damages to other organs [14]. Therefore, specific adjustments and additions

are needed before implementing this novel approach. Based on the review of existing studies, we hypothesised that the reactivation of the heart's endogenous regenerative ability through the induction of a hypoxic environment combined with the administration of 3, 3', 5-triiodo-L-thyronine (T_3) inhibitors could potentially be a more sustainable and effective method of treatment for myocardial infarction.

We reviewed literature from trusted scientific databases, including PubMed, Directory of Open Access Journals (DOAJ), and Scopus, to comprehend and synthesise information on the normal physiological development of the heart and the various regulators that induce heart maturation. We also searched for the results and limitations of regenerative medicine studies implementing hypoxia interventions in treating myocardial infarction. We then analysed the obtained information for potential gaps in knowledge that could be addressed by suggesting novel approaches. Studies that were not available in full text, were not written in English, and were not peer-reviewed were excluded from the reviewing process. Any disagreement or uncertainty was resolved through discussion among the authors.

Development of the Mammalian Heart

Similar to any other organ, mammalian cardiomyocytes proliferate during fetal development. However, the mammalian heart starts to lose its regenerative capacity as it matures [6]. The cardiomyocyte was inherently mononucleated during the early fetal stages. These mononucleated cardiomyocytes may undergo cytokinesis to produce more similar mononucleated cells or undergo terminal differentiation to form binucleated cells. The binucleated cardiomyocyte is larger in volume and rarely reenters the cell cycle for cytokinesis. Binucleated cardiomyocytes are phenotypically similar to adult cardiomyocytes, thus considered terminally differentiated and having lost their proliferative capacity [15]. The exact period in life when the mammalian heart starts to lose its proliferative capacity varies across species. Studies on sheep found that the proliferative cell cycle was generally higher during the early fetal stages. The terminal differentiation rate then exceeds the proliferation rate at around 115 to 125 days of gestation [16, 17]. In comparison, studies showed that terminal differentiation of mice cardiomyocytes occurred a few days after birth, whereas rat cardiomyocytes finished their terminal differentiation process approximately 14 days after birth [16]. Despite causing the loss of proliferative capacity, terminal differentiation into binucleated cells is a crucial process in normal heart development. A binucleated cardiomyocyte still undergoes growth by doubling its genetic material without dividing. Hence, binucleated cardiomyocytes are more specialised in mass expansion rather than proliferation [15].

The mechanism that induces the shift of human cardiomyocytes from hyperplasia to hypertrophy is mainly attributed to oxidative stress caused by the oxygen demand after birth. Intrauterine oxygen saturation is generally more hypoxic for the fetus, and oxygen-rich blood is primarily provided through maternal circulation [18]. The shift from cardiomyocyte proliferation to hypertrophy is an essential evolutionary process, as the developing heart size must match the body's oxygen demands [16]. When a newborn takes its first breath after birth, the heart starts to pump blood more vigorously with much higher oxygen saturation, and the pressure inside the heart increases. This condition causes the heart to experience a significant rise in energy demand as it becomes the primary provider of circulating oxygen throughout the body. The transition from the hypoxic intrauterine environment to the postnatal high-oxygen environment induces higher levels of reactive oxygen species (ROS). The high level of ROS then causes oxidative DNA damage. Studies have shown that mitochondrial-derived ROS is a primary cause of oxidative stress in postnatal cardiomyocytes and contributes to cardiomyocytes' cell cycle arrest [19].

Various signalling pathways and cell cycle regulators contribute to cardiac proliferation and differentiation. One such pathway is the Notch signalling pathway, which is essential in regulating proliferation, differentiation, and apoptosis in the developing heart. Studies have shown that almost half of proliferating cardiomyocytes have activated Notch1 in the nuclei [6, 20]. This is further supported by studies that showed that mutations in one of the Notch ligands led to the manifestation of heart defects, such as Tetralogy of Fallot, ventricular and atrial septal defects, aortic stenosis, and aortic coarctation [21]. Studies have identified neuregulin-1 (NRG1) as one of the molecules promoting cardiomyocyte proliferation through receptor tyrosine kinases – ErbB2, ErbB3, and ErbB4. NRG1 signalling was reported to stimulate DNA synthesis, karyokinesis, and cytokinesis. Studies demonstrated that the NRG1/ErbB signalling pathways modulate multiple downstream effectors, such as PI13K/Akt, MAPK/ErK, FAK, and Rac-PAK intracellular kinases [22]. These pathways contribute to the promotion of cardiomyocyte proliferation. For instance, the Rac1-PAK2 pathway was found to be essential for the regenerative capacity of the zebrafish heart [23]. Two other identified extracellular regulators that were found to promote cardiomyocyte cell cycle entry were follistatin-like 1 (Fstl1) and insulin-like growth factor (IGF2). Both of these extracellular regulators were shown to be produced by the epicardium [24, 25]. Studies have demonstrated that inhibiting these two regulators reduced cardiomyocyte proliferation[6].

In addition to signalling pathways, cell cycle regulators, including cyclins, cyclin-dependent kinases, and proto-oncogenes, are also essential in regulating cardiomyocyte proliferation. These regulators were found to be highly expressed in the fetal heart but not in the adult heart [6]. Cyclins are a family of essential cell cycle regulators that regulate the transition between cell cycle phases by binding to cyclin-dependent kinases (CDKs). One of the A-type cyclins, Cycline A2, has been shown to regulate cardiomyocyte proliferation by promoting the G1/S and G2/M transitions. Another essential type from the cyclin family is the D-type cyclins, including cyclin D1, D2, and D3. D-type cyclins bind with CDK4 or CDK6 to promote the transition of G1 to S phase. D-type cyclins are crucial regulators of cardiac proliferation during embryonic stages and have been found to decrease postnatally. D-cyclins' regulatory process will need to be halted at some point in fetal development to prevent overproliferation and shift the heart's development from hyperplasia to hypertrophy, which is necessary for postnatal viability. Numerous factors can induce the inhibition of D-cyclins. Among the three D-type cyclins, cyclin D1 is arguably the most discussed, as many studies have pointed out its regulatory factors [26].

3, 3', 5-triiodo-L-thyronine (T_3) Inhibition of Cyclin D1

Thyroid hormones are essential regulators of numerous metabolism processes, mitochondrial function, and thermogenesis. Thyroid hormones are synthesised as thyroxine (T_4), which is then converted to the active form of 3, 3', 5-triiodo-L-thyronine or triiodothyronine (T_3) by deiodinases. T_3 has a significantly higher binding affinity towards thyroid receptors than T_4 [27]. Many studies have indicated that thyroid hormones also contribute to the proliferation and differentiation of cardiomyocytes [28, 29]. During the second half of gestation, the mammalian fetus experiences a significant maturation process of the hypothalamic-pituitary-adrenal-thyroid axis [30]. Studies observed that the increase in T_3 plasma concentration in fetal sheep was slow during the last third of gestation. The T_3 plasma concentration then undergoes a rapid increase during the last week before parturition. This finding is similar to the human fetus, where T_3 plasma concentration is commonly unmeasurable until about 30 weeks of gestation. The T_3 plasma concentration then rises rapidly at term and another three- to six-fold during the first four to six hours of the postnatal period. This plateau period during fetal development coincides with the terminal differentiation phase of the heart [29].

Studies demonstrated that T_3 stimulated pathways that promoted cardiomyocyte differentiation and inhibited proliferation [28, 29, 31]. Studies also reported that the decrease in cardiomyocyte proliferative capacity associated with T_3 was mainly attributed to its inhibitory effects on cyclin expression [28]. In vivo studies that evaluated the impact of T_3 on fetal sheep cardiomyocytes by infusing T_3 during 125 to 130 days of gestation found that cardiomyocyte proliferation was reduced. In contrast, binucleation rates were increased with larger cells. Genes related to hypertrophy, such as the mammalian target of rapamycin (mTOR), atrial natriuretic peptide (ANP), and sarcoplasmic reticulum Ca^{2+}-ATPase 2A (SERCA2A), were also increased. Western blot analysis of ovine cardiomyocyte lysates showed that cyclin D1 levels were reduced two-fold after T_3 administration [28, 29]. One possible explanation is that T_3 stimulates MAPK/ErK and AKT/PKB pathways, reducing cyclin D1 [32]. T_3 affects the ErK and AKT signalling pathways via the intermediate protein Forkhead box O (FOXO). FOXO is a family of proteins consisting of FOXO1, FOXO3, FOXO4, and FOXO6. FOXO1, in particular, contributes to cell cycle arrest, energy metabolism, oxidative stress regulation, and apoptosis in cardiomyocytes. One of the downstream targets of FOXO1 included cyclin kinase inhibitors [33].

The findings from the abovementioned studies implied that inhibiting T_3 during the heart's endogenous state could preserve its proliferative and regenerative capacities for a more extended period. However, whether manipulating T_3 could induce regenerative effects on a fully differentiated adult heart remains unclear. The feasibility of this hypothesis depends on whether or not the cardiomyocyte maturation, cell cycle exit, and binucleation processes are reversible [28]. Therefore, manipulating T_3 could not solely be used as a potential treatment for myocardial infarction, as it needs a complementary approach to revert the cardiomyocytes to their early endogenous proliferative stages.

Hypoxia Induces Cell Cycle Re-entry in Mature Cardiomyocytes

Several studies have shown that inducing a hypoxic environment could revert cardiomyocytes to their endogenous proliferative state, thus promoting the regeneration of damaged cells [34-38]. As discussed earlier, there is a strong association between oxidative stress from the sudden increase in postnatal oxygen demand and cardiomyocyte proliferative capacity. The significant rise in postnatal mitochondrial energy metabolism increases ROS production and oxidative stress on cardiomyocyte DNA [19]. Studies that tried to comprehend the effect of hypoxia on the heart stemmed from the idea that, conversely, long-term systemic hypoxemia might reduce mitochondrial ROS production and induce cell cycle re-entry through the attenuation of oxidative DNA damage. The study by Nakada et al. [38] exposed groups of control and myocardial infarction

adult mice to a hypoxic condition similar to the summit of Mt. Everest (7% oxygen) for two weeks. This condition was achieved by gradually decreasing the oxygen tension by 1% daily from 20.9% ambient oxygen to 7% over two weeks. The study results from both groups showed decreased mitochondrial metabolism and oxidative damage in the cardiomyocytes. At the same time, terminally differentiated cardiomyocytes were also observed to re-enter the cell cycle. As for the myocardial infarction group, recovery of left ventricular systolic function and decreased fibrosis were also observed [34, 38]. Another study by Rigaud et al. [37], which implemented the same hypoxia protocol for their intervention, also found that hypoxia significantly increased the number of cardiomyocytes. However, an important consideration of this study was the increased mortality rate in both groups after three weeks of hypoxia exposure. This suggested that prolonged exposure to severe hypoxia is generally poorly tolerated in an otherwise normal mammal [37]. The study then conducted an additional test using moderate hypoxia condition of 10% oxygen combined with the administration of mitochondrial-ROS scavenger mitoTEMPO to address this issue. The results showed that there were also improvements in left ventricular function in the myocardial infarction group. However, no activity of cardiomyocyte proliferation was observed as a result of this intervention [34, 38].

After the success of these animal experiments, questions have been raised regarding the feasibility of translating them into human studies. A recent study named MyoCardioGen, conducted at the German Aerospace Center by Hönemann et al. [36], has proven that this translation is indeed possible. This study exposed four male human subjects to normobaric hypoxia conditions similar to 4500 meters altitude. The intervention was done by gradually decreasing the fraction of inspired oxygen stepwise by adding nitrogen for over 14 days before maintaining the achieved hypoxia condition for 4.5 days. The results showed improvements in left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and DNA repair in peripheral blood mononuclear cells (PBMCs). Hypoxia-induced pulmonary hypertension manifested during the intervention period but rapidly resolves after normoxia recovery [36]. However, similar limitations to animal experiments persisted in this study, where interventions with prolonged periods of hypoxia were not feasible due to its deleterious effects. In addition, this study only recruited highly selected subjects with previous altitude acclimatisation experience to tolerate the hypoxic intervention better, leading to a small study population. This inclusion criteria and the small study population could not be fully used to represent the general population [36, 39].

The Hypothesis of Combining Hypoxia and T_3 Inhibitors as a More Sustainable Approach

Considering that T_3 inhibition could result in sustained cardiomyocyte proliferative capacity during its fetal stages and the hypoxia-induced cell cycle re-entry approach discussed above, the combination of both may be a potential breakthrough in the treatment of myocardial infarction, as each could reinforce the other's shortcomings. The inhibition of T_3 in the adult heart did not seem to impose any regenerative effects since T_3 could only affect cardiomyocytes during their endogenous proliferative state [28]. This is where the hypoxia approach comes to light. The induction of a hypoxic environment was shown to revert differentiated cardiomyocytes to their endogenous proliferative state, enabling them to repair their damages. However, prolonged exposure to hypoxic conditions is not sustainable in patients [34, 36, 38]. Terminating the hypoxia intervention after cardiomyocytes have reverted to their endogenous state would lead to the rapid physiological maturation induced by T_3 [28, 29, 31]. Hence, administering T_3 inhibitors after the cardiomyocytes have been reverted in hypoxic conditions could prevent this process and enable patients to leave the hypoxic environment while preserving the heart's regenerative capacity. The administration of T_3 inhibitors could then be ceased after all the damaged areas of myocardial infarction have been replaced by new cardiomyocytes to induce their differentiation into healthy tissues and prevent overproliferation. This leads to a more sustainable approach as patients are not subjected to the deleterious effects of prolonged hypoxia exposure.

Conclusion

Heart diseases have been a global health issue and one of the leading causes of global mortality for decades. Myocardial infarction is one of the primary heart diseases and is strongly associated with permanent injury and sudden cardiac death. The adult heart's inherent nature as a non-regenerative organ due to its cardiomyocytes losing their proliferative and regenerative capacities at birth has made it a topic of interest for numerous studies in regenerative medicine. Recent studies have pointed out a novel approach to re-inducing cardiomyocytes into their endogenous proliferative state via hypoxic environments. However, the sole approach of hypoxia induction presents its limitations, such as unsustainable prolonged exposure and the infeasibility of being conducted on the general population without prior altitude acclimatisation experience. Therefore, we suggested that combining hypoxia to revert the cardiomyocytes to their endogenous proliferative state and administering T_3 inhibitors afterwards to maintain that particular state could be a more sustainable approach and a solution to the limita-

tions presented by previous hypoxia treatment studies. However, several other factors must be considered before this hypothesis can be translated into further human studies. These include other possible overlapping physiological cell cycle regulators that may contribute to the heart's maturation process, which phase of myocardial infarction is the most suitable treatment window, which T_3 inhibitor drugs are the most ideal for this approach, and how the administration of T_3 inhibitors could affect physiologic thyroid function.

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