Down’s syndrome and myocardial reperfusion injury

Susheel Kumar, Richard Jonas *

Children’s National Medical Center, 111 Michigan Avenue NW, Washington, DC 20010, United States

Received 10 June 2010; revised 19 August 2010; accepted 29 August 2010
Available online 9 September 2010

Abstract Down syndrome is known to be an independent risk factor for mortality after surgical repair of congenital heart anomalies. It is also associated with neurodegenerative disease and accelerated aging. The mechanism of the latter features has been attributed to abnormal handling of oxygen-free radicals as well as mitochondrial dysfunction. These properties also place the child with Down syndrome at a risk of an exaggerated myocardial ischemia/reperfusion injury.

A 6 month old child with Down syndrome is reported who suffered from obvious clinical ischemia/reperfusion injury following an uncomplicated repair of complete AV canal. Both intraoperative as well as postoperative echocardiography documented a satisfactory technical repair. After resting the heart on ECMO the child’s myocardial function returned to normal.

The mechanisms by which patients with Down syndrome are at risk of ischemia/reperfusion injury are reviewed. Future studies should focus on specific approaches for myocardial protection in the child with Down syndrome undergoing cardiac surgery.

© 2010 King Saud University. Production and hosting by Elsevier B.V. All rights reserved.
Down’s syndrome (DS) caused by an extra copy of genes on chromosome 21 is associated with a high incidence of congenital heart defects, mental retardation, early onset Alzheimer’s disease and an accelerated aging process among other deleterious phenotypes (Tiano et al., 2008; Pallardó et al., 2006). An imbalance in redox metabolism resulting in oxidative stress and tissue injury has been shown to be the basic defect underlying this disorder (Tiano et al., 2008; Pallardó et al., 2006). Gene-dose effect leads to elevated levels of superoxide dismutase-1(SOD-1) which results in an excess of reactive oxygen species (ROS) formation and consequent cell injury (Zigman and Lott, 2007). In recent years focus has shifted to abnormalities in mitochondrial function as an additional mechanism of cell injury (Conti et al., 2007; Prince et al., 1994; Arbuzova et al., 2002) in DS. Reperfusion following a period of ischemia is associated with generation of superoxide radicals and alterations in mitochondrial membrane (Yellon and Hausenloy, 2007). Although both redox metabolism and mitochondrial function are now known to be abnormal in DS, the issue of myocardial reperfusion injury either potential or real has not raised before. We report a case of myocardial reperfusion injury following open heart surgery in an infant with DS and discuss the possible mechanisms of the same.

1. Clinical summary

UL, a nearly 6 month old girl was diagnosed with Down syndrome and complete atroventricular canal at birth. Although surgical intervention for her congenital heart disease was initially planned at 3 months, it was delayed because of serious social reasons. She was medically managed with decongestive therapy for heart failure and weighed 5.3 kg at the time of operation. CXR showed cardiomegaly with pulmonary plethora. Electrocardiogram revealed prominent biventricular forces. Echocardiogram (ECHO) showed a complete atroventricular (AV) canal (Rastelli type A) with a large ventricular septal defect (VSD) and a large atrial component. Both the AV valves were competent. There was a bridging band of tissue between the superior and inferior common leaflets naturally dividing the AV valve into right and left components. In addition there was a moderate-sized ostium secundum defect.

Surgical repair of her congenital defect was undertaken under cardiopulmonary bypass. A standard midline sternotomy approach was used. Cardiopulmonary bypass (CPB) was instituted using aortic and bicaval cannulation. The patient ductus arteriosus was ligated soon after going on bypass. The patient was cooled to 28°C. Aorta was cross clamped and the heart arrested using antegrade cardioplegia (we use oxygenated St. Thomas crystalloid cardioplegia solution for myocardial arrest at our institution). The heart arrested satisfactorily with complete disappearance of electrical activity. The caval tourniquets were tightened and right atrium (RA) was opened by an oblique incision running parallel to the atroventricular groove. The ECHO diagnosis of CAVC type A was confirmed. The band of tissue between the bridging leaflets was used as a guide to demarcate the left from the right AV valve. Modified single patch technique was used for repair of the AV canal defect. The cleft in the left AV valve was repaired and both the atrial septal defects were closed using a single pericardial patch. The coronary sinus was placed on the left side of the patch. Half-dose cardioplegia was used intermittently at intervals of 20 min or earlier if there were signs of electrical activity. Rewarming was initiated towards the end of procedure. The heart was thoroughly deaired and the cross clamp was released with the cardioplegia site bleeding freely. The total cross clamp time was 39 min with two additional half doses of cardioplegia following the first full dose. At this point we noted that the myocardial perfusion was poor and the heart did not appear pink as it would normally do following release of cross clamp. It was hoped that this was a transient phenomenon and would rapidly improve. Epicardial pacing was used for variable heart block with intermittent periods of sinus rhythm. Upon complete rewarming, the child was weaned from cardiopulmonary bypass using 7.5 mg/kg/min of dopamine with systolic blood pressure in the 50 s and left atrial pressure between 12 and 15 mmHg. The total duration of cardiopulmonary bypass was 70 min. However, the myocardial perfusion continued to look poor with ST elevation in all the leads. There was some improvement in hemodynamics with return of sinus rhythm and escalation of dopamine support but with no difference in the color of the heart. About 30 min following weaning from CPB, the hemodynamics deteriorated and the child had to be placed back on CPB. A decision was made to rest the heart on Extracorporeal membrane oxygenation (ECMO) instead of attempting another wean with high pressors. A left atrial vent was placed to decompress the left heart. The perfusion of the heart remained concerningly poor through all this.

There was rapid return of pulsatility on ECMO. ECHO confirmed an adequate repair with mild to moderate left AV valve regurgitation. At the time of removal of left atrial vent 24 h later, we noted a significant change in the color of the heart. The heart appeared pink and well perfused for the first time following the operation and there was also a notable improvement in contractility. The patient could be easily weaned off ECMO within the next 24 h. She had an unremarkable post operative course following ECMO decannulation and was discharged home.

2. Discussion

Myocardial reperfusion injury is the injury caused to the myocardium by restoration of blood flow after an ischemic episode. This results in death or damage to the cardiac myocytes that were viable immediately before myocardial reperfusion. Myocardial reperfusion injury was first postulated by Jennings et al. in 1960. The injury that occurs to the myocardium on release of aortic cross clamp following cardioplegic arrest of the heart is a form of myocardial reperfusion injury. The reperfusion injury can manifest as four types of cardiac dysfunction.
Myocardial stunning denotes mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite the restoration of normal or near normal coronary flow. This is a relatively mild sublethal injury and results in global derangement of the mechanical properties of the heart. This heart usually recovers from this sort of injury within a few days to weeks.

The second type of injury is the ‘no reflow’ phenomenon which refers to the inability to reperfuse a previously ischemic region due to impedence of microvascular blood flow following restoration of blood flow. Reperfusion arrhythmias are the third type of injury and are often amenable to treatment. Lethal reperfusion injury causes death of the cardiomyocytes and is fatal.

Mediators of reperfusion injury (Fig. 1) have been well described (Yellon and Hausenloy, 2007).

1. **Oxygen paradox.** The reperfusion of ischemic myocardium generates harmful oxidative radicals termed reactive oxygen species (ROS) which can itself mediate myocardial injury. The ROS such as O$_2^-$, H$_2$O$_2$ and OH$^-$ also reduces the bioavailability of the intracellular signaling molecule like NO which has cardioprotective affects.

2. **Calcium paradox.** Reperfusion results in an abrupt increase in intracellular calcium secondary to sarcolemmal membrane damage and oxidative stress induced dysfunction of the sarcoplasmic reticulum. This resulting calcium overload induces cardiomyocyte death by causing hypercontracture of myocardial cells and opening of mitochondrial permeability transition protein (PTP).

3. **PH paradox.** The correction of pH following washout of lactic acid and activation of membrane channels contributes to reperfusion injury by activation of PTP.

4. **Inflammation.** Neutrophils are drawn into the injured area by the chemoattractants released by the myocardium following reperfusion. This is facilitated by the cell adhesion molecules. The neutrophils inflict damage by causing vascular plugging and release of degradative enzymes and ROS.

5. **Mitochondrial PTP.** The mitochondrial PTP is a nonselective channel of the inner mitochondrial membrane. Opening of the channel collapses the mitochondrial membrane potential and uncouples oxidative phosphorylation resulting in ATP depletion and death. The channel is closed during ischemia and opens with reperfusion in response to mitochondrial calcium overload, oxidative stress, restoration of physiological pH and ATP depletion.

### 2.1. Down’s syndrome

Studies suggest that multiple chromosome 21 genes affect protein synthesis, mitochondrial function and reactive oxygen species production, one carbon metabolism and cell adhesion (Conti et al., 2007). Mitochondrial function and ROS pathways have been targets of numerous studies on neurodegeneration in DS (Tiano et al., 2008; Pallardò et al., 2006; Conti et al., 2007; Prince et al., 1994; Arbuzova et al., 2002; Busciglio et al., 2002; Shukkur et al., 2006).

SOD-1 is a key enzyme involved in the metabolism of reactive oxygen species (ROS). Normally it protects against free radical injury by converting superoxide anion (O$_2^-$) into H$_2$O$_2$ which is further broken down by glutathione peroxidase to H$_2$O. SOD-1 level is markedly raised in DS as the gene for SOD-1 is located on chromosome 21. The increased level of SOD-1, a molecular...
marker of DS can lead to the accumulation of ROS like OH which can damage DNA, RNA, proteins and lipids. This oxidative stress has been implicated in the neuronal injury leading to mental retardation and early onset of Alzheimer's disease in DS (Brugge et al., 1992; Sinha, 2005). Oxidative stress also causes accelerated aging process (Pallardó et al., 2006).

On studying the gene expression profiles of the hearts of human fetuses with Down’s syndrome Conti et al. found that chromosome 21 gene expression was globally up regulated 1.5-fold. Interestingly, not all genes were equally upregulated and genes located on other chromosomes were also significantly dysregulated (Conti et al., 2007). Further analyses revealed down regulation of genes encoding mitochondrial enzymes and up regulation of genes encoding extra cellular matrix proteins. Reduction of mitochondrial enzyme activity has been reported in platelets from DS patients (Prince et al., 1994) as well as in astrocytes and primary cultures of fibroblasts (Arbuzova et al., 2002; Busciglio et al., 2002). Shukkur et al. elegantly demonstrated the contribution of mitochondrial dysfunction to neurodegeneration in a mouse mode of DS (Shukkur et al., 2006). Mitochondrial dysfunction has thus come to be increasingly recognized as an additional contributing factor to the pathology of DS.

Neutrophil chemotaxis and phagocytic activity have been proven to be adversely affected in DS (Zaldivar-Chiapa et al., 2005).

Thus it is easy to see how DS patients may respond differently to the reperfusion injury (Fig. 1) as ROS formation, mitochondria and leukocyte play a key role in it although we do not know how they may combine to produce a different response. In our case, we used the same standard cardioplegia at the same intervals as in any other patient. The heart responded well to the cardioplegic arrest and there were no signs of electric activity on ECG during the period of aortic cross clamp. Dearing of the heart was thorough before release of cross clamp and there were no signs of coronary air embolism. Mechanical dysfunction accompanied the pale color of the heart and both improved over a period of 24 h. The senior author of this paper has encountered a similar case of reperfusion injury in a Down’s syndrome with AV canal defect. In that case too, the patient recovered after being placed on ECMO.

DS patients form a significant proportion of those requiring repair of congenital heart lesions. The question of vulnerability open heart surgery as it did in our case. Awareness of this is important to recognize and deal with this form of reperfusion injury. More studies and research are required in this direction to understand this.

3. Conclusion

The underlying mechanisms operative in DS pathology may make them vulnerable to myocardial reperfusion injury following open heart surgery as it did in our case. Awareness of this is important to recognize and deal with this form of reperfusion injury. More studies and research are required in this direction to understand this.

References


