Word is currently not a viable option

Word Count: 2180Picture this. A man is involved in a severe car crash in Florida which has left him brain-dead with no hope for any kind of recovery. The majority of his vital organs are still functional and the man has designated that his organs be donated to a needy person upon his untimely death. Meanwhile, upon checking with the donor registry board, it is discovered that the best match for receiving the heart of the Florida man is a male in Oregon who is in desperate need of a heart transplant. Without the transplant, the man will most certainly die within 48 hours.

The second man’s tissues match up perfectly with the brain-dead man’s in Florida. This seems like an excellent opportunity for a heart transplant. However, a transplant is currently not a viable option for the Oregon man since he is separated by such a vast geographic distance from the organ. Scientists and doctors are currently only able to keep a donor heart viable for four hours before the tissues become irreversibly damaged. Because of this preservation restriction, the donor heart is ultimately given to someone whose tissues do not match up as well, so there is a greatly increased chance for rejection of the organ by the recipient. As far as the man in Oregon goes, he will probably not receive a donor heart before his own expires. Currently, when a heart is being prepared for transplantation, it is simply submerged in an isotonic saline ice bath in an attempt to stop all metabolic activity of that heart. This cold submersion technique is adequate for only four hours.

However, if the heart is perfused with the proper media, it can remain viable for up to 24 hours. The technique of perfusion is based on intrinsically simple principles. What occurs is a physician carefully excises the heart from the

donor. He then accurately trims the vessels of the heart so they can be easily attached to the perfusion apparatus.

After trimming, a cannula is inserted into the superior vena cava. Through this cannula, the preservation media can be pumped in. What if this scenario were different? What if doctors were able to preserve the donor heart and keep it viable outside the body for up to 24 hours instead of only four hours? If this were possible, the heart in Florida could have been transported across the country to Oregon where the perfect recipient waited. The biochemical composition of the preservation media for hearts during the transplant delay is drastically important for prolonging the viability of the organ. If a media can be developed that could preserve the heart for longer periods of time, many lives could be saved as a result. Another benefit of this increase in time is that it would allow doctors the time to better prepare themselves for the lengthy operation. The accidents that render people brain-dead often occur at night or in the early morning. Presently, as soon as a donor organ becomes available, doctors must immediately go to work at transplanting it.

This extremely intricate and intense operation takes a long time to complete. If the transplanting doctor is exhausted from working a long day, the increase in duration would allow him enough time to get some much needed rest so he can perform the operation under the best possible circumstances. Experiments have been conducted that studied the effects of preserving excised hearts by adding several compounds to the media in which the organ is being stored. The most successful of these compounds are pyruvate and a pyruvate containing compound known as perfluoroperhydrophenanthrene-egg yolk phospholipid (APE-LM). It was

determined that adding pyruvate to the media improved postpreservation cardiac function while adding glucose had little or no effect. To test the function of these two intermediates, rabbit hearts were excised and preserved for an average of 24.

5 1 0. 2 hours on a preservation apparatus before they were transplanted back into a recipient rabbit. While attached to the preservation apparatus, samples of the media output of the heart were taken every 2 hours and were assayed for their content. If the compound in the media showed up in large amounts in the assay, it could be concluded that the compound was not metabolized by the heart.

If little or none of the compound placed in the media appeared in the assay, it could be concluded that compound was used up by the heart metabolism. The hearts that were given pyruvate in their media completely consumed the available substrate and were able to function at a nearly normal capacity once they were transplanted. Correspondingly, hearts that were preserved in a media that lacked pyruvate had a significantly lower rate of contractile function once they were transplanted. The superior preservation of the hearts with pyruvate most likely resulted from the hearts use of pyruvate through the citric acid cycle for the production of energy through direct ATP synthesis (from the reaction of succinyl-CoA to succinate via the enzyme succinyl CoA synthetase) as well as through the production of NADH + H+ for use in the electron transport chain to produce energy. After providing a preservation media that contained pyruvate, a better recovery of the heart tissue occurred. Most of the pyruvate consumed during preservation was probably oxidized by the myocardium in the citric acid cycle. Only a small

amount of excess lactate was detected by the assays of the preservation media discharged by the heart. The lactate represented only 15% of the pyruvate consumed.

If the major metabolic route taken by pyruvate during preservation had been to form lactate dehydrogenase for regeneration of NAD+ for continued anaerobic glycolysis, rather than by the aerobic citric acid cycle (pyruvate oxidation), then a higher ratio of excess lactate produced to pyruvate consumed would have been observed. Hearts given a glucose substrate did not transport or consume that substrate, even when it was provided as the sole exogenous substrate. It might be expected that glucose would be used up in a manner similar to that of pyruvate. This expectation is because glucose is a precursor to pyruvate via the glycolytic pathway however, this was not the case. It was theorized this lack of glucose use may have been due to the fact that the hormone insulin was not present in the media. Without insulin, one may think the tissues of the heart would be unable to adequately take glucose into their tissues in any measurable amount, but this is not the case either.

It is known that hearts working under physiologic conditions do use glucose in the absence of insulin, but glucose consumption in that situation is directly related to the performance of work by the heart, not the presence of insulin. To further test the effects of the addition of insulin to the glucose media, experiments were done in which the hormone was included in the heart preservation media5-7. Data from those studies does not provide evidence that the hormone is essential to insure glucose use or to maintain the metabolic status of the heart or to improve cardiac recovery. In a

hypothermic (80C) setting, insulin did not exert a noticeable benefit to metabolism beyond that provided by oxygen and glucose. This hypothermic setting is analogous to the setting an actual heart would be in during transportation before transplant. Another study was done to determine whether the compound perfluoroperhydrophenanthrene-egg yolk phospholipid, (APE-LM) was an effective media for long-term hypothermic heart preservation3. Two main factors make APE-LM an effective preservation media.

(1) It contains a lipid emulsifier which enables it to solubilize lipids. From this breakdown of lipids, ATP can be produced. (2) APE-LM contains large amounts of pyruvate. As discussed earlier, an abundance of energy is produced via the oxidation of pyruvate through the citric acid cycle. APE-LM-preserved hearts consumed a significantly higher amount of oxygen than hearts preserved with other media. The higher oxygen and pyruvate consumption in these hearts indicated that the hearts had a greater metabolic oxidative activity during preservation than the other hearts. The higher oxidative activity may have been reflective of greater tissue perfusion, especially in the coronary beds, and thereby perfusion of oxygen to a greater percentage of myocardial cells. Another factor contributing to the effectiveness of APE-LM as a transplantation media is its biologically compatible lipid emulsifier, which consists primarily of phospholipids and cholesterol.

The lipid provides a favorable environment for myocardial membranes and may prevent perfusion-related depletion of lipids from cardiac membranes. The cholesterol contains a bulky steroid nucleus with a hydroxyl group at one

end and a flexible hydrocarbon tail at the other end. The hydrocarbon tail of the cholesterol is located in the non polar core of the membrane bilayer. The hydroxyl group of cholesterol hydrogen-bonds to a carbonyl oxygen atom of a phospholipid head group. Through this structure, cholesterol prevents the crystallization of fatty acyl chains by fitting between them.

Thus, cholesterol moderates the fluidity of membranes. 8The reason there are currently such strict limits on the amount of time a heart can remain viable out of the body is because there must be a source of energy for the heart tissue if it is to stay alive. Once the supply of energy runs out, the tissue suffers irreversible damage and dies. Therefore, this tissue cannot be used for transplantation. If hypothermic hearts are not given exogenous substrates that they can transport and consume, like pyruvate, then they must rely on glycogen or lipid stores for energy metabolism.

The length of time that the heart can be preserved in vitro is thus related to the length of time before these stores become too low to maintain the required energy production needs of the organ. It is also possible that the tissue stores of ATP and phosphocreatine are critical factors. It is known that the amount of ATP in heart muscle tissues is sufficient to sustain contractile activity of the muscle for less than one second. This is why phosphocreatine is so important. Vertebrate muscle tissue contains a reservoir of high-potential phosphoryl groups in the form of phosphocreatine.

Phosphocreatine can transfer its phosphoryl group to ATP according to the following reversible reaction: phosphocreatine + ADP + H+9ATP + creatinePhosphocreatine is able to maintain a high concentration of ATP

during periods of muscular contraction. Therefore, if no other energy producing processes are available for the excised heart, it will only remain viable until its phosphocreatine stores run out. A major obstacle that must be overcome in order for heart transplants to be successful, is the typically prolonged delay involved in getting the organ from donor to recipient. The biochemical composition of the preservation media for hearts during the transplant and transportation delays are extremely important for prolonging the viability of the organ. It has been discovered that adding pyruvate, or pyruvate containing compounds like APE-LM, to a preservation medium greatly improves post-preservation cardiac function of the heart. As was discussed, the pyruvate is able to enter the citric acid cycle and produce sufficient amounts of energy to sustain the heart after it has been excised until it is transplanted.

Increasing the amount of time a heart can remain alive outside of the body prior to transplantation from the current four hours to 24 hours has many desirable benefits. As discussed earlier, this increase in time would allow doctors the ability to better match the tissues of the donor with those of the recipient. Organ rejection by recipients occurs frequently because their tissues do not suitably match those of the donors. The increase in viability time would also allow plenty of opportunity for the organ to be transported to the needy person, even if it must go across the country.