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Evaluating the use of biomarkers for the diagnosis of myocardial injury in neonates

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SUMMARY

When most individuals think of a heart attack patient, they picture a middle-aged man or woman. While heart attacks are not as common in babies, they do occur. Currently, there are limited diagnostic strategies for cardiac complications and heart attacks in babies, which has resulted in high mortality rates. This literature review explores the use of specific proteins found in the blood, referred to as biomarkers, as a diagnostic tool for cardiac complications in babies. The review concludes that one particular biomarker, cardiac troponin, shows great promise in diagnosing cardiac injury in babies. This knowledge will help reduce the mortality rates of heart injury in babies. Future steps that need to be taken are exploring the limitations of cardiac troponin and improving diagnostic accuracy by using high sensitivity assays and umbilical cord blood to test biomarker levels.

ABSTRACT

Myocardial infarction is defined as the obstruction of blood flow to the heart, resulting in oxygen deprivation. While myocardial infarction in adults is common and has sufficient diagnostic strategies, there remain gaps in the diagnostic strategies for myocardial infarction in neonates. Presently, biomarkers such as creatine kinase-MB, brain natriuretic peptide, myoglobin, and troponin are believed to be potential diagnostic tools for neonatal myocardial infarction. This literature review explores the efficacy of biomarkers for early diagnosis of neonatal myocardial infarction. The review concludes that creatine kinase-MB, brain natriuretic peptide, and myoglobin do not serve as accurate biomarkers for myocardial infarction in neonates. However, cardiac troponins, in particular cardiac troponin I, have high sensitivity and specificity for diagnosing myocardial injury. Cardiac troponins experience rapid elevation upon myocardial injury, and they remain unaffected by gestational age and birth weight. In addition, they do not cross the placenta and are therefore intrinsic to the neonate. Future research should be conducted to verify the accuracy, sensitivity, and specificity of cardiac troponins as myocardial infarction biomarkers.

Keywords: Myocardial infarction, biomarkers, neonates, creatine kinase-MB, brain natriuretic peptide, myoglobin, troponin

INTRODUCTION

Myocardial injury, ischemia, and infarction occur when there is a lack of blood flow and oxygen supply to the myocardium (heart muscle) due to a coronary artery occlusion (**Figure 1**).[1] This can lead to necrosis and damage to the myocardium tissue.[1] Myocardial injury, ischemia, and infarction represent different durations of myocardium oxygen deprivation.[2] In particular, less than 20 minutes of myocardium oxygen deprivation results in myocardial injury, between 20 minutes and two hours results in myocardial ischemia, and over two hours results in myocardial infarction.[2]

While myocardial injury, ischemia, and infarction are common among adults, they are rare among neonates.[3] Myocardial infarction, injury, and ischemia have high mortality rates in neonates, with myocardial infarction having the highest mortality rate at 40 to 50%.[3] Early diagnosis of neonatal myocardial complications is challenging because the clinical symptoms are nonspecific.[4] Also, many of the diagnostic methods that are used for adult myocardial injury, ischemia, and infarction are invasive and inconclusive, and thus not sufficient for neonates.[4] For example, myocardial infarction in adults can be detected with electrocardiographic (ECG) changes.[5] In particular, the ECG readings of adults with myocardial

infarction have a pathological Q-wave, which is non-existent in neonates.[5] Q-waves in an ECG represent the left to right ventricular depolarization of the heart.[6] When the Q-wave is abnormally deep and wide, it reflects myocardial infarction.[6] Therefore, further research needs to be conducted so the appropriate diagnostic and management strategies can be developed for myocardial injury, ischemia, and infarction in neonates.

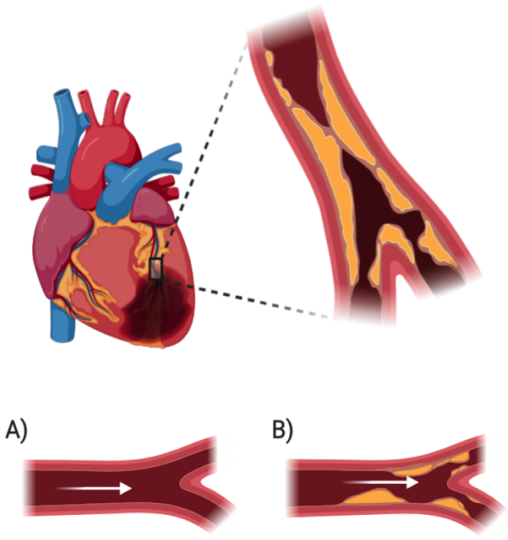

Figure 1. ***Blockage of the coronary artery leading to myocardial infarction.*** *(*A) *Normal Coronary Artery.* Oxygen and nutrients can flow to the heart tissue. (B) *Blockage of Coronary Artery.* Inflammatory and fatty substances adhere to the artery walls which form plaque. Plaque can form a clot (yellow) in the coronary artery, resulting in an insufficient supply of oxygen to the heart tissue. This can result in severe damage and even death to that portion of the heart. [Image made with BioRender]

Presently, biomarkers such as cardiac troponin, serve as a diagnostic tool for myocardial infarction in adults.[4] However, only a few studies have been conducted on the use of biomarkers for myocardial infarction in neonates.[4,7-10] This literature review will analyze the accuracy, sensitivity, and specificity of four biomarkers that have been used in previous studies for the diagnosis of myocardial injury in neonates: creatine kinase-MB, natriuretic peptides, myoglobin, and troponin.[4,7-10]

CREATINE KINASE-MB

Creatine kinase is a protein found in many tissues of the body, such as skeletal, cardiac, and brain tissues.[11] Creatine kinase-MB (CK-MB) is an isoenzyme of creatine kinase and is found mostly in the heart muscle.[11] Following injury to the heart, CK-MB in the myocardium is released into the bloodstream and can be measured.[9] However, based on a thorough analysis of previous studies, it is evident that serum CK-MB should not be used as a biomarker for myocardial injury in neonates.[9,12] This can be attributed to a few reasons.

The primary reason is that CK-MB elevation has low cardiac specificity as neonatal CK-MB is derived from both myocardial and skeletal muscle.[7,12] Hence, it is difficult to determine if serum CK-MB is high due to skeletal or myocardial injury. In addition to this, CK-MB has been shown to be elevated in healthy neonates. Almeida et al. illustrated that healthy neonates had elevated CK-MB levels in their first 24 hours of living, followed by a significant decline to approximately half their initial values.[7] This result suggests that high neonatal levels are due to stress or injury from delivery and skeletal involvement.[7] CK-MB is also affected by gestational age, birth weight, and mode of delivery.[13] In particular, CK-MB levels increase with decreasing gestational age and birth weight.[8] Furthermore, neonates who are delivered vaginally have significantly higher levels of CK-MB than neonates who are delivered by cesarean section.[14] It is important to note that unlike other biomarkers such as troponin I, CK-MB is capable of traversing the placenta.[7] Therefore, high levels at birth can be of maternal origin and result in the overestimation of CK-MB neonatal levels.[7]

While CK-MB was previously believed to be a specific biomarker for myocardial injury, many studies show contradictory and interesting results.[9] For example, myocardial injury and infarction in neonates have been shown to be caused by asphyxia.[15] In particular, myocardial damage occurs in up to 73% of asphyxiated neonates.[9,16] Asphyxia can also cause renal failure, which causes CK-MB to lose its specificity for myocardial injury when renal problems arise, resulting in false positive rates of 20 to 30% for myocardial injury.[10,17] This is supported by the results of a study performed by Sadoh et al.[10] The study included a control group of asphyxiated neonates without myocardial or renal injury and three experimental groups: a group of neonates with myocardial injury, a group with renal injury, and a group with combined myocardial and renal injury.[10] The results illustrated that CK-MB was significantly higher in the renal injury group and combined injury group than in the control group ($P<0.0001$ and $P=0.006$, respectively).[10] However, CK-MB was not significantly higher in the myocardial injury group than in the control group ($P=0.55$).[10] The results of this study suggest that CK-MB is an effective biomarker for renal injury, but not myocardial injury.

CK-MB should not be used as a neonatal myocardial injury biomarker because the elevation of serum CK-MB concentration takes longer compared to other biomarkers.[9] For example, CK-MB takes three to eight hours to rise after myocardial injury, whereas troponin I typically rises within two to three hours of myocardial injury.[9,17]

Overall, CK-MB is not an accurate biomarker for myocardial injury in neonates because it has low cardiac specificity, it is affected by gestational age and birth weight, and its elevation is delayed compared to other biomarkers.

BRAIN NATRIURETIC PEPTIDE

Brain natriuretic peptide (BNP) is a myocardium hormone that is released into the bloodstream upon ventricular filling and myocardium stretching following injury to the heart.[7] It is believed that BNP does not cross the placenta and, therefore, neonatal BNP levels are intrinsic.[7] Despite the advantages of using an intrinsic biomarker, there are certain downfalls to the diagnostic use of BNP as highlighted below.

A study conducted by Jiang et al. demonstrated that BNP is not a predictor of myocardial injury in neonates.[9] This study used the current Chinese diagnostic criteria to identify myocardial injury in the neonates.[9] The criteria includes perinatal hypoxia, abnormal electrocardiogram readings for the ST-T wave for two to three days, and clinical manifestations such as bradycardia, low blunt heart sounds, and signs of poor circulation.[9] This criteria differs from other studies as other studies focus only on clinical manifestations.[4,9] Focusing solely on clinical manifestations has limitations because atypical cases, in which the neonate does not display clinical symptoms, can occur and result in delayed diagnosis.[4,9] There was no significant difference in serum BNP levels 12 hours after birth between the myocardial injury group and non-myocardial injury group ($P=0.398$).[9] These results suggest that serum BNP levels do not rise following cardiac injury and therefore cannot be used as a cardiac biomarker. In addition to its lack of elevation following cardiac injury, BNP has a couple more limitations. Neonates who develop myocardial dysfunction from asphyxia are often exposed to hypoxia.[9] A hypoxic environment can increase the expression of the ventricular BNP gene, which can lead to increased levels of plasma BNP that mimic acute myocardial injury.[9] Therefore, increased BNP levels can be a reflection of hypoxia rather than myocardial injury. That being said, if the hypoxic environment is controlled for, researchers can overcome this limitation and BNP can be used as an indicator of neonatal myocardial injury. This is shown by a clinical study performed by Zhu and Nie.[18] The researchers found that serum NT-proBNP was significantly higher in the asphyxia with myocardial injury group than the asphyxia with non-myocardial injury or control groups ($P<0.01$).[18] These results suggest that, when a hypoxic environment is controlled for, BNP can be used as a biomarker for neonatal myocardial injury.

Furthermore, BNP has low specificity to myocardial injury as BNP levels rise in healthy neonates.[7] Almeida et al. showed that healthy neonates have a significant rise in BNP levels during the first 24 hours of their life.[7] This rise is attributed to the ventricular overload during the transition from fetus to neonate.[7] In addition, the left and right ventricles release BNP to reduce the work done by the heart.[7] This release is known to help with the adaptation to extrauterine life and to achieve physiological homeostasis.[7] Thus, the elevation of BNP in neonates occurs to aid with growth, and may not be reflective of a myocardial injury.

Overall, BNP is not an accurate biomarker for myocardial injury. BNP serum levels do not always rise following myocardial injury, BNP is limited in hypoxic environments, and it lacks specificity for myocardial injury as levels also rise in healthy neonates.

MYOGLOBIN

Myoglobin is a protein that binds oxygen and is located in the heart and skeletal muscles.[19] Upon injury to the muscle, myoglobin is released into the bloodstream and can be measured.[19] Very few studies have focused on the use of myoglobin for the diagnosis of myocardial injury in neonates.[9,20] One study, conducted by Jiang et al., showed that there was no significant difference in myoglobin levels between neonates with and without myocardial injury.[9] The study concluded that myoglobin is found in a wide range of muscle tissues and is therefore not a specific marker for myocardial injury.[9]

In addition to this, a study performed by Kaur et al. showed that myoglobin levels are strongly correlated with renal failure and renal tubular damage.[20] This further reduces the specificity of myoglobin because asphyxia, previously noted as a common cause of myocardial injury, can also cause renal failure.[10] As a result, this can lead to false positives of myocardial injury in neonates with asphyxia.

Overall, myoglobin lacks specificity for myocardial injury as it is found in many muscle tissues of the body and is correlated with renal injury.

TROPONIN

Troponin I, C, and T are regulatory proteins found in the troponin-tropomyosin complex and play an essential role in skeletal and cardiac muscle contraction.[21] Troponin C has one isoform that is found in both skeletal and cardiac muscle, whereas troponin I and T have isoforms that are distinct between the skeletal and cardiac muscle.[21] As a result, cardiac troponin I and T (cTnI and cTnT) are often used in the diagnosis of myocardial damage in adults. If cTnI and cTnT are found in the extracellular space, such as the serum, it is reflective of myocardial injury (**Figure 2**).[4]

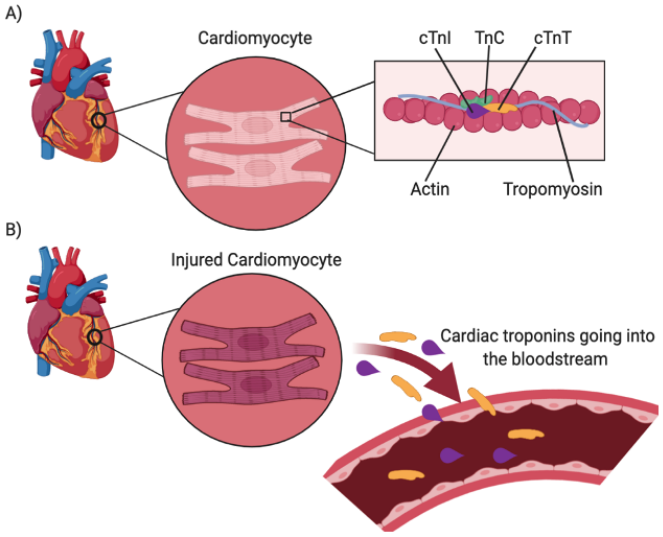

Figure 2. ***Structure of troponin complex in the myocardium.*** *(*A) Normal cardiomyocyte (B) Damaged cardiomyocyte resulting in the release of cardiac troponin T (yellow) and cardiac troponin I (purple) into the bloodstream. [Image made with BioRender]

One study, conducted by Tarkowska and Furmaga-Jabłońska, tested the efficacy of cTnT as a biomarker for myocardial injury in neonates.[4] Blood samples were taken from neonates with an identified heart defect and cTnT levels were evaluated using a Roche CARDIAC T Quantitative test, which consists of two monoclonal antibodies that are specific to cTnT.[4] They concluded that newborns with heart defects had significantly higher levels of cTnT than the control group (P=0.035).[4] In addition, cTnT had high specificity and sensitivity.[4]

The results of this study are supported by Joseph et al. who measured serum cTnT levels in asphyxiated neonates with and without myocardial injury.[13] They discovered that asphyxiated neonates with myocardial injury had significantly higher levels of cTnT (P=0.0001).[13] In addition, they found that cTnT had a sensitivity and specificity of 92.4% and 94.1%, respectively, using a threshold value of 0.1145 ng/mL.[13] Therefore, it is evident that cTnT has the potential to be used as an accurate diagnostic tool for myocardial injury in neonates.

Jiang et al. conducted a study to test the diagnostic ability of cTnI. High sensitivity cardiac troponin I (hs-cTnI) was measured using a chemiluminescence immunoassay (Abbott Laboratories) with a detection limit of 1.1-1.9 ng/L.[9] At 12 hours postnatal, hs-cTnI was significantly higher in the myocardial injury group than the non-asphyxia control group (P<0.001) and the non-myocardial injury with asphyxia group (P=0.016).[9] It is important to note that seven days after birth, there were no significant differences in serum hs-cTnI among the three groups.[9] This indicates that hs-cTnI should be used for the diagnosis of myocardial injury closer to 12 hours after birth.[9] Jiang et al. also determined that the sensitivity and specificity of hs-cTnI, using a cut-off value of >0.087 ug/L, was 55.6% and 95.5%, respectively.[9]

Overall, troponins are preferred over other biomarkers for a few reasons. First, cardiac troponins have a large diagnostic window due to their intracellular compartmentalization. They rapidly elevate in the serum two to four hours after the initial injury, peak after 12 hours, and can remain elevated for up to ten days.[4,7] Second, they are not affected by gestational age, mode of delivery, sex, or birth weight.[13] Finally, cardiac troponins have large molecular masses that are unable to freely diffuse across the placenta.[13] In particular, cTnT and cTnI have molecular masses of 37 kDa and 24 kDA, respectively.[13,22] As a result, the neonatal cardiac troponin levels that are measured are not affected by maternal levels.[13]

CARDIAC TROPONIN I VS. CARDIAC TROPONIN T

While cardiac troponin I and T are both regulatory proteins of the troponin-tropomyosin complex, they differ in many ways, such as their molecular weight, half-life, and intracellular compartments.[4] There seems to be controversy surrounding which troponin is more accurate. One reason why cTnT may be preferred is that cTnI is more sensitive to covalent and enzymatic modifications (i.e., phosphorylation and methylation), which decrease its binding capacity to specific antibodies in the assay system.[13] This could lead to reduced signals in the assay and under-

estimation of cTnI levels.[13] However, most studies have a preference for cTnI as it is believed to have better diagnostic ability for neonatal myocardial injury than cTnT. This is because cTnT levels are affected by adrenaline administration during cardiopulmonary resuscitation.[23] Hence, this reduces the value of cTnT as a biomarker for myocardial injury in neonates as resuscitation is often necessary postnatally. A second reason is that the expression of the cTnT gene is more complex, as it contains four alternatively spliced transcripts. This makes it difficult to determine the immunoassay to use for the detection of the protein. Finally, Immer et al. illustrated that cTnT levels were higher in neonates with postoperative renal failure, which can lead to false positives of myocardial injury.[24] Therefore, cTnI has the advantage of not being affected by renal problems.

FUTURE STEPS

After thorough analysis of all biomarkers, it is evident that cardiac troponins, in particular cTnI, have high sensitivity and specificity for diagnosing myocardial injury. Future steps that need to be taken include finding methods to enhance its diagnostic ability. For example, using the most appropriate assay and blood sample type to measure troponin levels. With new technological advances, enhanced assays are being developed which allow for more accurate results. Presently, venous blood samples are the most common blood sample type; however, recent advances in the field have shown promise for other blood sample types such as umbilical cord blood. Improving diagnostic ability will enable early diagnosis of myocardial injury so preventative measures can be taken to reduce cardiac complications.

ASSAY TYPE

Currently, there are many different assays available for measuring cardiac troponins. The first assay was developed by Cummins et al. in 1987 and, since then, cTnI assays have become 1000 times more sensitive.[22,25]Assays are classified based on the sample percentage of healthy subjects that exceed the assay's limit of detection (LOD).[22] Low sensitivity assays have the highest LOD, whereas high sensitivity assays can have an LOD that is an order of magnitude lower than low sensitivity assays.[22,26] High sensitivity assays are a recent development; therefore, more studies need to be performed using these assays to determine and verify diagnostic ability.

BLOOD SAMPLE TYPE

In addition to the assay type, the blood sample type also affects diagnostic ability. Neonates are often subject to acute renal failure and, therefore, have limited renal clearance of biomarkers.[27] This can result in the elevation of specific biomarkers using venous blood samples. However, umbilical cord blood samples do not have this issue with renal clearance and is therefore a more accurate indicator of perinatal injuries.[26,27] For example, a recent study in press by Mondal et al. was conducted to determine a reference interval for hs-cTnI in the umbilical cord blood of neonates using a hs-cTnI assay.[26] Mondal et al. concluded that hs-cTnI levels in the umbilical cord blood of neonates are comparable to those of an adult reference population.[25] These findings contradict the results of current literature which state that troponin I levels in neonates are higher than adult troponin levels.[26] This result can be attributed to the difference in the type of blood sample that was collected in the Mondal et al. study.[26]

Furthermore, the studies referred to in this literature review were conducted at later stages in neonatal life, resulting in elevation of specific biomarkers due to other neonatal-related injuries. However, using umbilical cord blood largely avoids this. Overall, it is important to consider the type of blood sample taken.

CONCLUSION

To conclude, CK-MB, BNP, and myoglobin do not serve as accurate biomarkers for myocardial injury in neonates. CK-MB is limited due to its low specificity for myocardial injury, as well as its delayed elevation following myocardial injury. BNP has low specificity for myocardial injury and levels can be affected by a hypoxic environment. Myoglobin lacks specificity for myocardial injury as it is found in numerous muscle tissues of the body. Overall, studies have shown that cardiac troponins are the most accurate biomarkers for myocardial injury. Troponins experience rapid elevation upon myocardial injury, they remain unaffected by gestational age and birth weight, and they do not cross the placenta and are therefore intrinsic to the neonate. In particular, cTnI shows great promise as it has high specificity and a large range of immunoassays can be used for its detection. However, further research needs to be conducted using high sensitivity assays and umbilical cord blood. Also, the limitations of cardiac troponins need to be further explored, and their specificity and sensitivity need to be verified.

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