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Determination of Myocardial Function Using Heart Accumulated Radiopharmaceuticals

C. C. D. Kulathilake, M. Jayatilake, T. Takahashi

***Abstract*—**The myocardium is composed of specialized muscle which relies mainly on fatty acid and sugar metabolism and it is widely contribute to the heart functioning. The changes of the cardiac energy-producing system during heart failure have been proved using autoradiography techniques. This study focused on evaluating sugar and fatty acid metabolism in myocardium as cardiac energy getting system using heart-accumulated radiopharmaceuticals. Two sets of autoradiographs of heart cross sections of Lewis male rats were analyzed and the time- accumulation curve obtained with use of the MATLAB image processing software to evaluate fatty acid and sugar metabolic functions.

***Keywords*—**Autoradiographs, fatty acid, radiopharmaceuticals and sugar.

I. Introduction

HEART is hollow muscular organ which is composed of cardiac muscle [1]. Cardiac muscle mainly consists of three layers which are endocardium, myocardium, and pericardium [2]. The myocardium is composed of specialized cardiac muscle found only in the heart and that is the place where the cardiac energy system taken place [3].

Several fuel resources are used for production of mitochondrial ATP (Adenosine Triphosphate) in cardiac muscle fibers. However, cardiac energy producing systems mainly rely on fatty acid and sugar metabolic processes [4]. In this case 60% of ATP produces from fatty acid oxidation, 35% of ATP produces from sugar (mainly glucose) oxidation and rest of 5% obtain from lactic acid, amino acid and ketone bodies processes [2]. Therefore, fatty acids serve as the primary energy source in the myocardium under the normal conditions. In plasma, there are several kinds of non-esterified fatty acids available that are taken up by myocardium, then these are esterified to triglycerides and incorporated into two lipid granules [3].

There are several kinds of heart disease conditions in modern society. One of the commonest heart failure condition occur from normal heart functioning stage to acute heart failure stage (myocarditis) and then it can be converted to chronic heart failure stage (myocardial fibrosis). Myocarditis is an inflammation of the myocardium due to various causes such as viral infections, rheumatic fever, exposure to radiation and certain medication. It has no symptoms in most of cases [5]. Then, myocarditis condition can be converted into myocardial fibrosis conditions due to progression of the diseased condition. The consequence of extracellular cardiac matrix remodeling is known as cardiac fibrosis [6].

In this study, we present the evaluation of fatty acid metabolic and sugar metabolic functions and their correlation during heart failure conditions of acute heart failure stage (myocarditis) and chronic heart failure stage (myocardial fibrosis).

The objectives of this study were acquire heart cross section autoradiographs using normal and dilated cardiomyopathy heart cross sections of rats, evaluate changes of fatty acid and sugar metabolic functions in various condition of heart using autoradiographs and heart accumulated radiopharmaceuticals and analyze the correlation between fatty acid and sugar metabolic function within the myocardium using autoradiographs.

II. Methods

The experiments were performed at Radioisotopes Center in Niigata University, Japan. Lewis male 74 rats were obtained and then the healthy subjects were selected based on normal range of monitored blood pressure and blood flow rate values. Then cardiac myosin which was obtained from the pig's heart was injected randomly selected 37 rats to generate dilated cardiomyopathy disease as which is shown in Fig. 1 and the group was labeled as dilated cardiomyopathy rat group or Chronic Heart Failure rat group: (CHF). The remaining rats were labeled as normal rat group. Both groups were injected with radiopharmaceuticals of ^{131}I-9MPA 15-(p-(^{131}I iodophenyl)-9-methylpentadcanoic acid) (fatty acid) and ^{14}C-2DG (2-deoxy-D-(1-^{14}C) glucose) (sugar mixture) (Fig. 2).

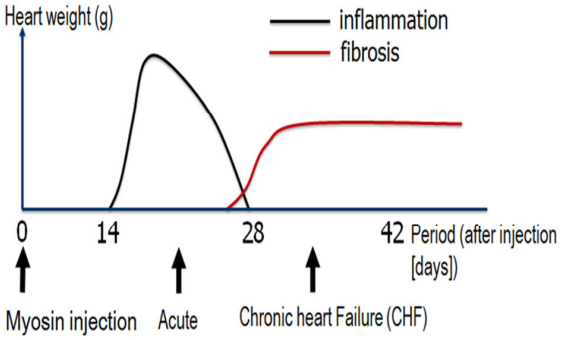
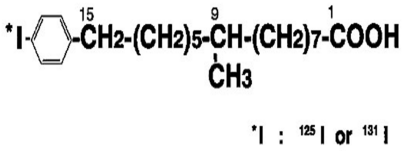


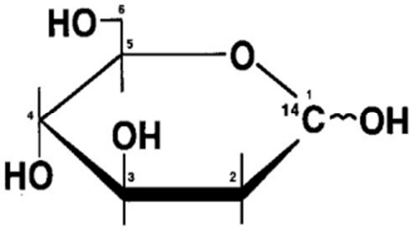
Fig. 1 Produced dilated cardiomyopathy disease schedule

C. C.D. Kulathilake, M. L. Jayatilake are with the Department of Radiography-Radiotherapy, Faculty of Allied Health Sciences, University of Peradeniya, Peradeniya, Sri Lanka (phone: +94719337633; e-mail: cdchathu@gmail.com, jayatiml@pdn.ac.lk).

T. Takahashi is with the Department of Radiological Technology, School of Health Sciences, Niigata University, Niigata, Japan (e-mail:takatosi@clg.niigata-u.ac.jp).



(a) Labeled fatty acid [^{131} I]-9MPA (15-(p-(^{131}I iodophenyl)-9 methylpentadcanoic acid)



(b) Labeled sugar [^{14}C]-2DG(2-deoxy-D-(1-^{14}C) glucose)

Fig. 2 Radiopharmaceuticals

Next the body weight of each rat was measured. Then a part of heart in CHF stage was excised from rats at aimed time such as 5, 10, 30, 60 and 120 (min) and normal stage was excised from rats at aimed time of 10 and 60 (min) after injecting the radiopharmaceuticals. All the heart cross sections were derived through the ventricle region of the heart and thickness of every single heart cross sections were obtained as 20 (μm) then tissue were weighted. Next two sets of autoradiographs were prepared using heart cross sections for evaluation purposes. Fujifilm BAS (Bio Image Analyzer System) image plates (IP) were covered with a polythene wrapper. The heart cross sections of CHF and normal rat group were obtained at 5, 10, 30, 60,120(min) and 10, 60 (min) respectively. Then those heart cross sections were placed on the labeled Fujifilm BAS image plates. Next the IPs were placed inside of the double sided cassettes and cover with a plane paper. The closed cassettes were placed inside the lead shielded box for desired time. Fujifilm BAS image plates were removed and placed in the Fujifilm BAS 5000 image analyzer in dark environment after 72 hours. Then autoradiographs were obtained in digital format (Fig. 3). Then obtained images were processed and analyzed using MATLAB image processing software.

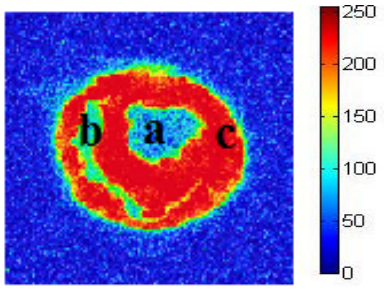


Fig. 3 Typical heart autoradiograph—preprocessed image (I-131 9MPA) (a) Left ventricle (b) Right ventricle (c) Myocardium

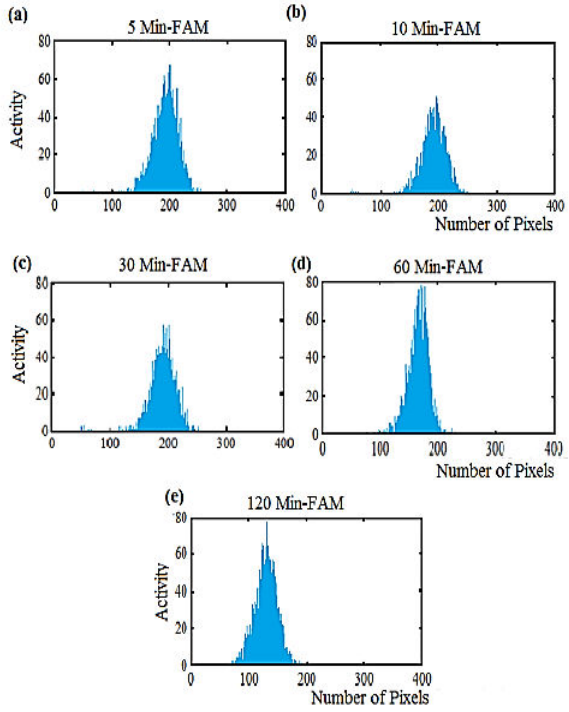


Fig. 4 Histograms of fatty acid metabolism (FAM) at different time points (a) 5 Min (b) 10 Min (c) 30Min d) 60 Min (e) 120 Min

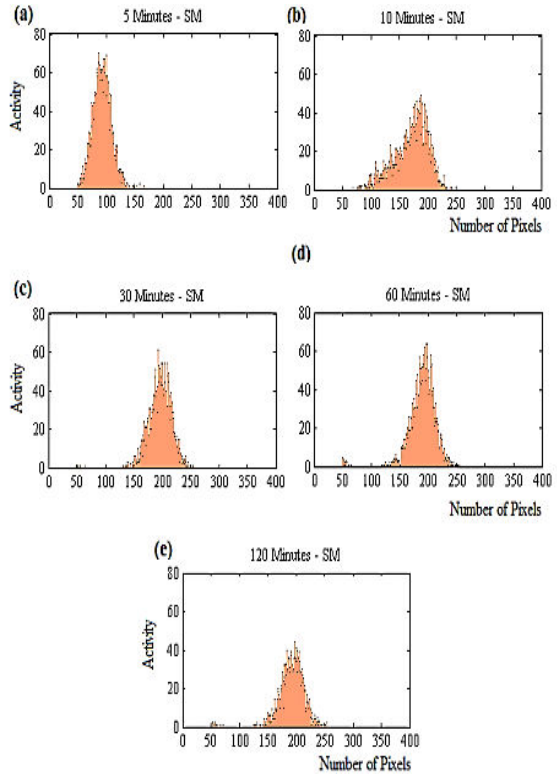


Fig. 5 Histograms of sugar metabolism (SM) at different time points (a) 5 Min (b) 10 Min (c) 30Min d) 60 Min (e) 120 Min

Region of Interests (ROI) on multiple image slices were drawn encompassing heart cross sections. Then average tracer accumulation values were obtained for each time point using the pixel values within the ROIs. Then tracer accumulation curve against time was plotted for both fatty acid and sugar metabolism.

Time accumulation-curve for FAM was generated using mean values of histograms of fatty acid metabolism (Fig. 4). Histogram was plotted activity versus number of pixels within the autoradiographs (ROIs). Mean values of fatty acid accumulation are equal to the mean value of metabolic activity (y axis) of the FA (fatty acid) and FA accumulation was obtained at different time points of 5,10,30,60 and 120 Min in CHF phase.

Time accumulation-curve for SM was generated from mean values of histograms of sugar metabolism (Fig. 5). Histogram was plotted activity versus number of pixels within the autoradiographs (ROIs). Mean values of Sugar accumulation are equal to the mean value of metabolic activity (y axis) of the Sugar and Sugar accumulation was obtained at different time points of 5,10,30,60 and 120 Min in CHF phase.

III. Results

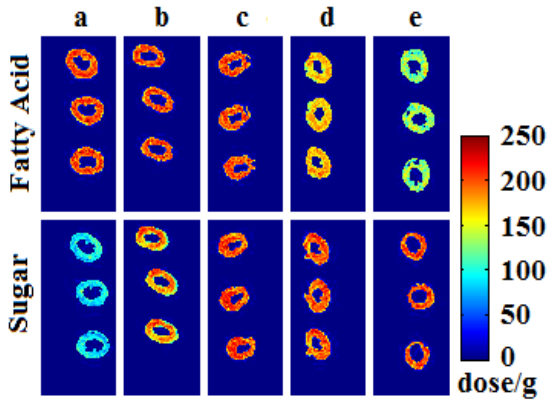


Fig. 6 Autoradiographs related to the fatty acid and sugar metabolism in CHF stage at different time periods

Fig. 6 shows the autoradiographs which were obtained at the different times points, (a) 5, (b) 10, (c) 30, (d) 60 and (e) 120 (min) in related to the fatty acid and sugar metabolic process. It is reported that the normal heart functioning phase in fatty acid metabolism, variation of both heart cross section diameters was insignificant but tracer accumulation were slightly decrease with respect to the time. However in CHF phase, myocardium fatty acid accumulation reduce from ~250 to ~100 (dose/g) from 5 (min) to 120 (min).Again it is noticed that the normal heart functioning phase in sugar metabolism, myocardium tracer-accumulation slightly increased from 5 (min) to 120 (min). However, at the CHF phase, it increased from ~50 ~250 (dose/g) within the given time points (see Fig. 6). Fig. 7 illustrated the time-tracer accumulation curve for Fatty acid (blue) and Sugar metabolic processes (red).

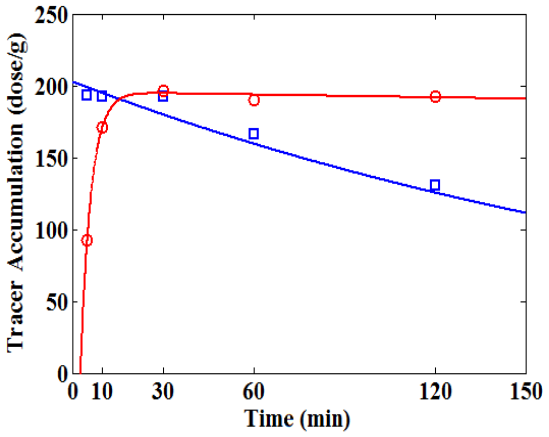


Fig. 7 Time-tracer accumulation curve for Fatty acid and Sugar metabolic processes

The tracer accumulation of I-131 9MPA exponentially decays with respect to the time. That implies fatty acid metabolic process decrease exponential with time in CHF phase (shown in blue curve in Fig. 7). The tracer accumulation of C-14 2DG exponentially growth with respect to the time. That means, sugar metabolic process increases exponential with time in CHF phase (shown in red curve in Fig. 7).

IV. Discussion

This study represents an attempt to evaluate myocardial function of the rats' heart with use of heart accumulate radiopharmaceuticals. In this study, myocardium function basically evaluated by using fatty acid metabolic process and sugar metabolic process. However, total myocardial function is not relies on these two processes. However, 60% of cardiac energy system relies on fatty acid metabolic process and 35% relies on sugar metabolic process, other 5% of cardiac energy system relies on lactic acid, amino acid, and ketone bodies processes. Therefore, 95% of cardiac energy getting system has been evaluated by this study. Other 5% of cardiac energy system can also be evaluated with use of heart accumulated radiopharmaceuticals which can be bound to lactic acid, amino acid and ketone bodies and lactic acid, amino acid compounds. Therefore, such a study can be used to evaluate total cardiac energy system on myocardium. The autoradiographs which were used to evaluate fatty acid and sugar metabolic processes were obtained axial images through the ventricle of the hearts including both left and right ventricles. Because more thickened area of the heart is ventricle area and the left ventricular area is most thickened area from both left and right ventricles. Left ventricular area is most important area for heart which is used to distribute required amount of blood throughout the body including vital organs within acceptable pressure. Therefore, there is a high probability to occurring diseases in that area. Drugs are considered as one of most important aspects to cure diseases. Nowadays several drugs are used to cure myocardium diseases in the Medical as well as Veterinary fields. This study can be used to check whether

how drugs are behaved and affected to the cardiac energy system, myocardium and during myocardium disease conditions. These drugs such as Carvedilol, Pivalic acid, and MIBG (metaiodobenzylguanidine) can be injected to the rats along with the radiopharmaceutical injection. Both rats and human are categorized as mammalian. Mammalian heart is basically consisted of endocardium, myocardium and pericardium and there are several similarities as well as differentiation between humans' and rats' heart in physiologically, anatomically and embryonic origin. Although this study has been completed using rats, results of this study can be indirectly applied for human models. From normal heart functioning stage to chronic heart failure stage fatty acid metabolic process is decreases than normal condition and sugar metabolic process is increases than normal condition. Therefore doing further analysis, fatty acid and sugar can be used as bio-indicator or bio-marker to detect and diagnose some disease conditions.

V. Conclusion

In normal conditions, myocardium gets a lot of energy by fatty acid metabolic process, yet in diseased conditions like CHF, the fatty acid metabolic process was damaged and myocardium becomes to use sugar as energy source instead of fatty acid. At that time fatty acid metabolic process decrease with time as an exponential decay and sugar metabolic process increases with time as an exponentially.

Acknowledgment

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