CHAPTER 1

INTRODUCTION:

Cardiac Diagnostic: Spectroscopy and Image aspect

Highlights of the Chapter

- *A brief overview of the cardiac disease and diagnosis*
- *Problems with Spectroscopy and Image-based Cardiac Diagnosis*
- *Objectives, contribution, and organization of the thesis*

1.1 Brief overview of the cardiac diseases and diagnostics

According to World Health Organization (WHO), the major cause of death worldwide is cardiovascular disease (CVD). In 2016 approximately 17.9 million people died because of CVD which represents 31% of global death[1]. Out of these, 85% of deaths are due to heart attack or stroke. 75% of deaths due to CVDs occur in mid-income and low-income countries. Out of the 17 million deaths due to non-communicable diseases in 2015 of patients under the age of 70, 82% are in low- and middle-income countries, and 37% are caused by CVDs. In 2016, the estimated prevalence of CVDs in India was estimated to be 54.5 million[2], [3]. One in 4 deaths in India is now because of CVDs with ischemic heart disease and stroke responsible for >80% of this burden. Overall, cardiovascular diseases contributed 28.1% of the total deaths and 14.1 % of the total DALYs in India in 2016, compared with 15.2% and 6.9%, respectively, in 1990[4]. In 2016, there was a nine times difference between states in the DALY rate for ischemic heart disease, a six times difference for stroke, and a four-time difference for rheumatic heart disease. 23.8 million prevalent cases of ischemic heart disease were estimated in India in 2016, and 6.5 million prevalent cases of stroke, 2.3 times increase in both disorders from 1990[5][6].

Recognition of CVDs is the first and most important step in the treatment and management of the patients by the healthcare system. Timely diagnosis of cardiovascular disease plays a vital role in the effective management of high-risk patients. Early diagnosis of heart disease not only helps in providing adequate life-saving therapeutic intervention but also reduces the load on the healthcare system. Increased risk of death due to CVDs demands for accurate, rapid, sensitive, and reliable, affordable detection systems.

Several diagnostic modalities are developed for heart function analysis like biomarker monitoring. Broadly, cardiac function analysis modalities can be subdivided into Image-based systems, Signal based systems, and biomarker-based systems. Imaging techniques include but are not limited to Cardiac Magnetic Resonance Imaging (CMRI)[7], Echocardiography[8], and Computed tomography[9]. Signal Processing techniques include Phonocardiography (PCG)[3] and Electrocardiography (ECG)[10] while Biomarker based techniques include detection of cardiac-specific biomarkers detection like troponins (cTnI, cTnT, Myoglobin, etc.). Biomarkers specific to the heart are established to be identifiers of CVDs whose concentration varies as the physiological and pathological condition of the cardiac environment varies.

1.2. Outline of Spectroscopy based cardiac diagnosis

A biomarker or biological marker is a quantifiable indicator of a pathophysiological condition or state. Biomarkers are measured to examine and evaluate the biological process using blood, urine, or any soft tissue. A biomarker is an important tool for improved identification of patients on high-risk CVDs. Several biomarkers are identified for CVDs within blood serum or plasma such as Cardiac Troponins, NT-proBNP, C-reactive protein (CRP), Myoglobin, etc.

Several techniques have been developed for the early diagnosis of stroke and other CVDs. Techniques such as surface plasmon resonance (SPR)[11], immunoassays[12], enzyme-linked immunosorbent assay (ELISA)[13], surface-enhanced Raman spectroscopy (SERS)[14], field-effect transistor-based methods[15], and liquid chromatography are commonly used for the quantification of biomarkers. Drawbacks of these methods include sample-specific preparation, long processing time, and the requirement of central laboratories. Recently, the main focus has been on point-of-care tests (POCT) for portability, small sample size, fast detection, and high accuracy.

Requirements of ideal cardiac biomarker

High concentration, absence in other tissue, rapid release after myocardial injury, homogeneous distribution in heart, release proportional to damage, presence in plasma for the diagnostic window but not so long that recurrent injury cannot be identified, suitable to analyze are required characteristics for a cardiac biomarker to be ideal. For a biomarker to fulfill these requirements, the characteristics a biomarker must have:

- Small molecule biomarkers are better as they reach circulation more rapidly
- A cytosolic protein is released more rapidly than structural proteins after injury and so an earlier increase of level in plasma is obtained
- Macromolecule of high solubility reaches plasma faster
- Low local degradation of the molecule after release as this may lead to the low amount of detectable molecule than released due to injury
- Specificity to the myocardium.

Spectroscopy in Cardiac Diagnosis

The phenomenon of inelastic scattering of monochromatic light when incident on a sample is the Raman effect. The elastically scattered light is known as the Rayleigh effect where light scatters with the same energy as incident light whereas inelastic light scatters with a different wavelength. This difference in energy of incident light and scattered light is called Raman shift which provides the fingerprint signature of the molecule.

Surface-enhanced Raman spectroscopy is an advanced method of Raman spectroscopy where signal intensity enhancement is observed. Intensity enhancement in SERS is now agreed to be dominantly contributed by electromagnetic enhancement mechanism. Chemical enhancement is also attributed to SERS intensity which is primarily based on the charge-transfer mechanism. Total SERS enhancement is the product of enhancement due to electromagnetic mechanisms and chemical mechanisms[16], [17]. In highly optimized systems, an enhancement by a factor of ~ 10^{10} to 10^{14} can be achieved.

SERS provides Raman signal enhancement but a lot of experimental consideration is required to be tuned for obtaining such enhancements. Substrate plays a vital role in the enhancement of Raman signal intensity in SERS. Substrates range from nanorods to colloidal solutions of noble metal having tunable plasmon resonances. The excitation source is also an experimental parameter that must be selected carefully. The source must be able to excite enough plasmon resonance. Theoretically, maximum enhancement is obtained when the laser is tuned to the peak surface resonance of the substrate. The success of SERS is highly dependent on the interaction of absorbed molecules and surface plasmon substrate typically gold or silver nanostructures.

1.3. Outline of Image-based cardiac diagnosis

Cardiac function analysis can play an important role in the determination of abnormality in the heart such as but not limited to valve abnormality and cardiac tumor as it provides detailed structural information of the heart. Also, several parameters for the heart can be calculated (Ejection fraction, stroke volumes) which further assist in the diagnosis of heart diseases like Hypertrophic cardiomyopathy. Many instruments based on imaging modality have been developed for monitoring the condition of the heart like Cardiac Magnetic resonance imaging (CMRI) [7], Echocardiography[18], Ultrasound, and Computed tomography[9]. Cardiac Magnetic resonance imaging (CMRI) is considered a state-of-the-art method for Cardiac function analysis.

Cardiac Magnetic resonance imaging is considered the gold standard for non-invasive cardiac function analysis due to its 3D capabilities and high spatiotemporal resolution. It had been already proved to be an invaluable tool in the diagnosis of complex cardiomyopathies. Cardiac Magnetic resonance not only helps in the visualization of cardiac anatomy but also allows to know the functional behavior of the heart. Clinical implications of cardiac MRI are:

- Quantify coronary blood flow
- Measurement of ventricular volumes, wall thickness, and other parameters.
- Quantify myocardial infarction size.
- Myocardial viability
- Measure blood flow in the myocardium

Cardiac MRI has unique aspects as the heart is in continuous motion. MR imaging technique is although a very fast technique and can generate images in fractions of heartbeat, clinical biomedical images require high spatial resolution, good contrast, requires several heartbeats to complete the image. Cardiac MRIs are mostly gated with the patient's ECG such that a small portion of the image is captured in each heartbeat. This result is a clear cardiac image without distortion or motion blur.

CMRI provides information for evaluating the structure of the heart and surrounding blood vessels, assessing blood flow to cardiac muscle, determining the functioning of the heart's chambers and valves, evaluating infection, and detecting tumors. But for accurate extraction of detailed information about the condition of the heart from CMRI, precise segmentation of different parts of the heart is required. Manual segmentation provides accurate results but it is a time-consuming process and requires expert personnel and still there exists a probability of error in segmentation due to intra and inter-observer variability. Thus, an accurate and automated segmentation process is required for improving the clinical application of CMRI in heart diagnosis while remaining time-efficient.

In recent years, the application of deep learning methods in medical image processing such as lesion classification and segmentation increased considerably. The application of deep learning methods in Cardiac MRI segmentation was very much limited until 2013. In 2015, Kaggle organized the Second Annual Data Science Bowl in which a lot of applications of deep learning methods were presented to the community. Since then, a huge number of deep learning methods were applied for CMRI analysis. Deep learning methods used until 2018 were summarized by Bernard et. al. Several variants of U-Net, Dense Nets, novel localization, and semantic segmentation network, motion estimation and segmentation networks, and different novel variants of fully connected networks had been proposed by different authors. In the MICCAI 2017 Automatic Cardiac Division challenge, 9 out of 10 proposed methods are a deep learning-based method and out of 9, 8 were variants of U-Net. Although from the above discussion, it is clear that one can have quantifying parameters for LV/RV without the need for segmentation, cardiac diagnosis is based on physiological parameters and so the need for segmentation maps is required to evaluate the cardiac quantification parameters.

1.4. Problems with Spectroscopy and Image-based cardiac diagnosis

Spectroscopy based diagnosis

Biomarkers are small molecules that can be quantified and help in the prognosis of the heart condition. Concentration above a certain value for biomarkers represents the changes of occurring of cardiac event in near future or certain heart condition is developed recently. Several spectroscopic methods had been used by different research groups still limitations exist in the method. Major limitations are:

- Method specific and tedious sample preparation
- Long processing and result time
- Requirement of central lab
- Lack of standardization
- Lack of prognosis capabilities and lower detection of limit

Image-based diagnosis

Cardiac function analysis provides several information related to heart structure and helps in the diagnosis of several pathological conditions like hyper cardiomyopathy. But to accurately extract this information from cardiac function analysis-based modalities especially MRI, accurate segmentation is of the utmost importance. Despite several hardware and software advancements in recent years, several limitations exist like the requirement of ground truth, Image intensity and contrast inhomogeneity, and others. Major difficulties in Image-based diagnosis, regarding MRI, are as:

- Poor contrast between myocardium and surrounding structures
- Brightness heterogeneities in LV and RV chamber due to blood flow
- Presence of trabeculae and papillary muscles with intensity similar to the myocardium
- Inherent noise due to motion and heart dynamics
- Shape and intensity variability of heart structures
- Presence of banding artifact

1.5. Thesis Objectives

The principal objective of the thesis is to improve methods of cardiac diagnostic by improving two of the most used aspects: Image-based diagnosis and Microendoscopy based diagnosis. In this view, this thesis aims to fulfill the following objectives.

- Design and optimization of Raman probe for Cardiac troponin I detection.
- Validation of the use of spectroscopic methods in Cardiac troponin I detection.
- Spectral signal processing to extract more accurate and quantitative information from the signal.
- Development of an algorithm for more accurate segmentation of CMRI to improve feature extraction for diagnosis of the cardiac pathological condition.
- To pave a way towards unsupervised segmentation of cardiac images to exploit the availability of vast unannotated biomedical image data for better diagnosis.

1.6. Thesis Contribution

This thesis contributes to the necessary theory and implementations for the image as well as spectroscopy-based diagnostic improvement in cardiac abnormality detection as listed below.

- Video-rate microendoscope is fabricated using 3D printed mounts and 1st harmonic oscillation for fiber cantilever for faster scan and custom-made micro-optics for imaging.
- Active-passive detection of cTnI in gold nanoparticles is shown using UV-Vis spectroscopy.
- Application of Double-density dual-tree complex wavelet transform is shown for efficient and minimum distortion processing to remove noise and spikes in spectroscopic signals.
- For the imaging approach, three different methods were developed to accurately segment CMRI which in turn will augment the cardiac diagnosis namely transfer learning-based method, modified U-Net with noise stifler block to segment noisy MRI, and cascade of conventional method and deep learning method for weakly supervised segmentation of CMRI.

1.7. Thesis Organization

The thesis is divided into 5 parts and comprises a total of 8 chapters. The remaining thesis has been organized in the following manner to provide detailed information regarding the ideas that have been mentioned beforehand.

- **Part-I** is titled "Background"; contains Chapter 1 (current), Chapter 2, and Chapter 3.
  - **Chapter 2** presents theoretical background of probe fabrication for spectroscopy, methods used for cardiac biomarker quantification, and signal processing for denoising of spectroscopy signals.
  - **Chapter 3** presents the theoretical background and literature review regarding cardiac diagnosis using image modality. This chapter also discusses a brief overview of the methods used previously and their utilization in cardiac diagnosis.

- **Part-II** is titled "Spectroscopy- based Diagnosis" contains Chapter 4, and Chapter 5.

- ○ **Chapter 4** presents the fabrication of a video-rate microendoscope probe for *in vivo* imaging of internal organs in live and fabrication of probe for spectroscopic detection of biomarkers.
- ○ **Chapter 5** presents the application of UV-Vis spectroscopy, FTIR, and Raman spectroscopy for detection of cardiac biomarker. This chapter also presents the algorithm for denoising and spike removal from spectroscopic signals.

- **Part-III** is titled "Image-based Diagnosis"; contains Chapter 6 and Chapter 7.
  - ○ **Chapter 6** presents the implementation of a cascade of conventional clustering methods and a deep learning-based method to segment cardiac MR images in weakly supervised mode. One of the main limitations of the currently available method to segment is the requirement of masks drawn by experts. The proposed method paves a way to segment the Left Ventricle in CMRI without the need for a mask and with minimal user interference.
  - ○ **Chapter 7** presents the implementation and performance of algorithms for segmentation of cardiac magnetic resonance images:
    - A transfer learning-based segmentation of Cardiac MR images with encoder modified U-Net and Feature Pyramid Network for fast and easy convergence of segmentation network while requiring fewer resources and providing comparatively better results from well-established state-of-the-art methods.
    - Modified U-Net with Noise stifler block to accurately segment noise-free as well as noisy cardiac MR images.

  Part-II ends with feature extraction of cardiac MR Images using above stated methods and then classifying the ACDC dataset in pathophysiological classes for cardiac diagnosis.

Classification methods used are machine learning-based and primarily used here are Random Forest and K-Nearest Neighbor.

- **Part-IV** is titled “Closure”; contains Chapter 8 and Chapter 9.
  - **Chapter 8** summarizes the findings and contributions of the thesis and highlights major achievements.
  - **Chapter 9** discusses the scope of work in future directions based on the studies performed till now.

- **Part-V** is titled “Accomplishments”; contains the publications related to the thesis work and the achievements during the doctoral studies.

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