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Characterization of Cardiac Troponin I Raman Signature in Bovine Serum Albumin and Human Blood Serum for the Potential Diagnosis of Myocardial Infarction

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Abstract

Cardiac troponin I is one of the most specific and widely used biomarkers of myocardial infarction. Prompt recognition of elevated troponin concentrations in the blood is essential to the diagnosis and management of acute coronary syndrome (ACS). Raman spectroscopy allows for detection of the unique cTnI Raman signature based on quantitative measurement of wavelength and intensity of in elastically scattered light from molecules. For the first time in the literature, we have successfully characterized and verified the unique Raman signature of mouse cardiac troponin I protein in Bovine Serum Albumin and Human Blood Serum. Our findings potentiate technological advancement towards point-of-care testing measurement of cardiac biomarkers, which can be employed, potentially more rapid than conventional ELISA assays, in the outpatient setting and emergency departments for routine detection of cardiac troponin I elevation from patients suspected of suffering from acute coronary artery syndrome.

Keywords: Cardiac biomarker; Raman spectroscopy; Myocardial infarction; Biophotonics; Point of care testing; Acute coronary syndrome

Introduction

Detection of cardiac biomarkers in addition to characteristic symptoms and electrocardiographic abnormalities constitute current diagnostic guidelines for Acute Coronary Syndrome (ACS) [1]. An elevation in concentrations of the protein biomarker, cardiac troponin I (cTnI), has diagnostic, management, and prognostic implications [2,3] and is routinely quantified in emergency departments. In symptomatically identical patients, an elevation in cTnI concentration may warrant patient hospitalization, immediate catheter angiography, and possible therapeutic intervention, as opposed to supportive management and potential same day discharge [4].

Despite their recognition as the current gold standard [5], limitations exist in detecting elevated myocardial infarction biomarker concentrations [6] such as the need to obtain blood samples, lack of inter-laboratory standardization, and time delays that can surpass an hour for laboratory processing. Assay sensitivity in current laboratory-based automated platforms limits detection of circulatory cTnI concentrations to post symptomatic levels [7], despite systemic circulation at lower concentrations several hours prior. Moreover, population based observational studies in patients suspected of ACS exhibit prevalent hesitation to promptly contact primary care physicians, as well as delayed hospital presentation as late as a median of 4 hours after symptom onset [8,9]. Unfortunately, comparatively higher myocardial infarction biomarker concentrations suggest prolonged ischemia and irreversible cardiac damage.

Prompt diagnosis and intervention is the cornerstone of management in ACS, and advances in diagnostic technology using animal and human models are recently emerging [7,10,11]. Raman spectroscopy is based on quantitative measurement of wavelength and intensity of in elastically scattered light from molecules. The Raman scattered light occurs at wavelengths that are shifted from the incident light by energies of molecular vibrations. This vibration can be observed in either the Infrared (IR) or Raman spectra. While IR spectroscopy measures the absorption of infrared light by the sample, Raman spectroscopy measures the scattered light.

The objective of this study is to utilize biophotonic technology to characterize the unique Raman signature of recombinant mouse cTnI in Bovine Serum Albumin (BSA) and Human Blood Serum (HBS). The importance of selecting recombinant mouse cTnI is the striking structural similarities between human and mouse cTnI [12]. The potential clinical application of this physiological signature, as governed by its distinct molecular structure, is to serve as a highly specific point-of-care testing (POCT) for prompt diagnosis of ACS.

Research Significance

Despite medical breakthroughs in the management of cardiovascular diseases, Coronary Artery Disease (CAD) remains a global leading cause of mortality [13]. Alarming statistics persist despite widespread implementation of interdisciplinary public health measures aiming at the prevention and early treatment of heart diseases. Particular vulnerability of myocardial cells to inadequate blood perfusion and the critical role of the heart as a central organ translate into ischemic-reperfusion injury and significant morbidity and mortality from myocardial infarction (MI). The spectrum of pathophysiological changes associated with ACS commence hours prior to objective symptoms as specific myocardial infarction

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biomarkers are released into the systemic circulation secondary to cardiac myocyte ischemia and lysis. Severe ischemia lasting as short as minutes followed by reperfusion may lead to myocyte necrosis and irreversible damage. Rapid detection of MI biomarkers with results available in minutes permits prompt decision-making and better patient management, particularly in cases with inconclusive findings from electrocardiography [8]. Considering that early medical intervention during ischemic attacks to the heart is of paramount importance and can prevent further tissue damage, early detection of such biomarkers can be lifesaving.

This paper briefly describes the principles behind Raman Spectroscopy and our experimental approach, followed by an illustration of the unique cTnI Raman signature, and a discussion of the findings.

Methods and Materials

Raman spectroscopy

In Raman spectroscopy, a laser beam is used to irradiate a sample over the Ultra-Violet-visible (UV-visible) and near-infrared-region (NIR) spectrum (200 to 900 nm). The scattered beams are also at the UV-visible-NIR region and consist of two parts:

1. Rayleigh scattering which is strong and has the same frequency as the incident beam; and

2. Raman scattering, which is very weak and has a frequency of higher or lower than the incident beam.

These discrepancies in frequency of incident beam and Raman scattering are unique to each molecule, enabling the identification of a molecule from its Raman signature. A Stokes shift is defined as a Raman scatter frequency that is lower than the incident beam frequency. Similarly, an Anti- Stokes is a Raman scatter frequency, higher than the initial incident beam.

Raman spectroscopies are done in the UV-visible and NIR region. Therefore, IR and Raman are considered complementary in that certain vibrations will be solely Raman active (e.g., totally symmetric vibrations), while others being exclusively IR active. Covalent bonds are generally very strong in Raman while ionic bonds are strong in IR. This feature of Raman makes it especially advantageous for our studies of proteins as it can adequately detect the vibration of the covalent bonds between amino acids. Another advantage of Raman over IR spectroscopy is that most proteins in the body are in an aqueous solution and water is inconveniently a strong absorber of IR. In contrast, water is a weak Raman scatterer. Raman scattering can be done in aqueous solutions using a single recording and it is not necessary to change gratings, beam splitters, filters and detectors in obtaining a Raman spectrum over a wavenumber range as wide as from 4000 cm^{-1} to 50 cm^{-1}. The reason being both the incident and the scattered beams are in the UV-Visible-NIR range of 200-900 nm. Therefore, Raman spectroscopy in the 200-900 nm wavelength range can be manipulated by a single set of optical elements. Furthermore, water is relatively transparent to light in all or most of this wavelength range and this inherent quality makes Raman a superior choice for most bio scientific applications.

Identifying the Raman signature of cTnI using a partial least square regression (PLSR) model

Identifying analyte concentrations from an optical signal may require a simple linear model, such as models used in Evanescent Field sensors, where a clear linear relationship is observed [14,15]. However, in most cases of label-free detection in which a signature of a molecule at low concentration is being detected (absorption, reflection, or Raman spectroscopy) and other molecules with interfering signatures also exist, a linear relationship may not be as apparent. In such cases, regression analysis and sometimes noise reduction are required to identify the dependency and extract the correlation [16,17]. Inverse Least Square (ILS) methods, such as multiple linear regression (MLR), principal component regression (PCR), and partial least square (PLS), are commonly used and are suitable for spectroscopy signals. MLR finds factors that can correlate the Raman spectra with concentration. PCR finds factors with most variance in Raman spectra. However, we need to find wave numbers that capture the most variance in the Raman spectra and have the strongest correlation with cTnI concentrations. Because PLS is a combination of MLR and PCR, it is able to find the factors that can both capture variance in Raman spectra and achieve strong correlations between Raman spectra and cTnI concentrations. Therefore, the Partial Least Square Regression (PLSR) model is most effective method for our application.

Identification of the dependency between cTnI concentrations and its Raman spectra was achieved by using a PLSR model, which captures maximum variations in Raman spectra that best explains variations in cTnI concentration [11]. PLSR reduces the dimensionality of the system to a given number of components or latent variables. For each of these latent variables, a weight vector that describes the dependency of that component to the original variables in the Raman spectra is calculated. The PLSR weights manifest how strongly each variable in the Raman spectra can explain the variation in concentrations and therefore, the PLSR weight is a measure of variations in the signal that correlates strongly with a particular concentration [18,19].

Each latent variable makes a contribution to the model. To evaluate the contribution of each latent variable, one quick measure is to calculate the percentage variance of the concentrations explained with the addition of each latent variable. Afterwards, the weight vector corresponding to the latent variable that explains the most variations has the indication of the strongest correlation between Raman spectra and the corresponding cTnI concentration. Moreover, preprocessing data with baseline correction and removing orthogonal noises reduces the complexity of the model, meaning that the weights corresponding to a smaller LV number explains stronger correlation with the concentrations and the corresponding wave numbers. In our application, for each set of data, we first identified the contribution of each regression component in explaining the variations in concentrations, and subsequently plotted the weights corresponding to the component with maximum contribution. That weight vector will manifest as the segments of the Raman spectrum that have the strongest correlation with cTnI concentrations.

Recombinant mouse cTnI preparation

Protein over-expression of recombinant mouse cTnI was performed as previously described [20]. In summary, recombinant mouse cardiac protein subunits were expressed in *E. coli*. BL21 (DE3) (Novagen) cells with the cTnI gene in the kanamycin resistant pSBET vectors. Our method of cTnI purification has also been previously reported [20,21] with the following modifications: the cTnI- containing cell lysate was made to 25% saturation with ammonium sulphate, and the supernatant was obtained after centrifugation at 27,000 g for 30 minutes (Beckman JLA16.25) at 4°C. The supernatant was dialyzed overnight against 2-3 changes of four liters of buffer A (6 M Urea, 25 mM TEA-HCl, 1 mM EDTA, and 1 mM DTT at pH 7.5) and then loaded onto a CM sepharose® column (XK26, Amersham Biosciences), which was

previously equilibrated with buffer A. Cardiac TnI was eluted at 50-60% of a linearly increasing gradient of 0-0.5 M NaCl in buffer B (6 M urea, 25 mM TEA- HCl, 1 mM EDTA, 1 mM DTT and 0.5 M NaCl at pH 7.5). If the purity was not satisfactory as determined by 12% Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), all fractions containing cTnI were pooled together and further purified by DEAE fast flow column (GE Healthcare). The fractions containing cTnI were dialyzed against buffer C (6 M urea, 20 mM Tris-HCl, 1 mM EDTA, and 0.5 mM DTT at pH 8.0). Other contaminant proteins remained bound to the column while cTnI eluted from the flow through and wash fraction. CTnI was then dialyzed extensively against 5 mM ammonium bicarbonate, lyophilized, and stored at -20°C.

The Raman spectra of two sets of analytes are measured and analyzed:

1. cTnI in BSA, HCl and CTNC
2. cTnI in human blood serum

Results

For each set of data, we first identified the contribution of each regression component in explaining the variations in concentrations, and then plotted the weights corresponding to the component with maximum contribution. That weight vector indicates the segments of Raman spectra that have the strongest correlation with cTnI concentrations.

cTnI signature

Figure 1 illustrates the percentage variation of cTnI concentration explained versus the number of PLSR components or latent variables, both for the case of BSA and human blood serum. In the spectra for cTnI in BSA without preprocessing, the fourth LV explains the maximum variations, whereas the first latent variable would include the maximum explanation after data preprocessing to remove noise and baseline variations. After data preprocessing with baseline correction and OSC (Orthogonal Signal Correction - a method allowing for the elimination of background noise), the first latent variable explains more than 97.8% of the variance in concentrations.

cTnI in BSA and in serum

Figure 2 shows the PLSR weights for the Raman spectra of cTnI in BSA corresponding to their most significant latent variable concluded from Figure 1a. Figure 2a shows the weight for data without preprocessing and its most significant latent variable (4th LV). Figure 2b shows the weight vector for the 4th LV, after the Raman signal is smoothed and corrected for baseline variations. Figure 2c shows the weight for data after preprocessing and its most significant latent variable (1st LV).

As can be seen in the PLSR weights for cTnI in BSA without any preprocessing, peaks around wave numbers 1595 cm^{-1} and 1790 cm^{-1} are observed. However, they are masked by significant noise. After preprocessing data and removing orthogonal noises, two obvious peaks appear in the weighted signal (Figures 2 and 3). In the following section, it will be shown that these same peaks are observed in the other set of data with cTnI in blood serum.

Figure 3 shows the PLS weights for Raman spectra of the second set of data cTnI in Blood Serum corresponding to their most significant latent variable concluded from Figure 1b. Figure 3a shows the weight for data without preprocessing and its most significant latent variable (2nd LV). This set of Raman spectra exhibited a lot of baseline

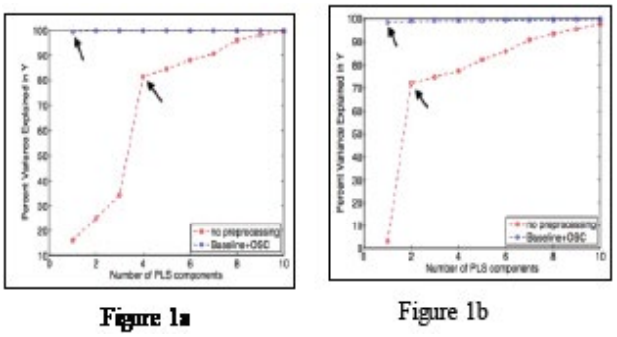

Figure 1: Example Percent variation in concentration explained as a function of number of latent variables in the model. The arrows indicate the latent variable that explains most of the variations. (a) cTnI in BSA, HCl, and cTnC; (b) cTnI in human blood serum.

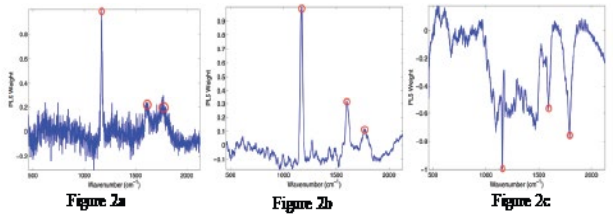

Figure 2: PLS weights of the most significant, LV for the Raman spectra of cTnI in BSA. The red circles from left to right correspond to the wavenumbers 1160 cm^{-1}, 1595 cm^{-1}, 1790 cm^{-1}, respectively. (a) PLS weights of 4th LV, for the raw data; (b) PLS weights of 4th LV, for the smooth and baseline corrected data; (c) PLS weights of 1st LV, for the preprocessed data.

variations. Therefore, correcting for baseline variations and smoothing the signal, the weight vector for the second latent variable can be found and is shown in Figure 3b. Figure 3c shows the weight for data after preprocessing and its most significant latent variable (1st LV).

We have measured the Raman spectrum of cTnI in BSA. Reviewing the PLSR weight in all those measurements suggests a strong correlation between the existence of cTnI and certain wave numbers in the Raman spectrum. Thus, cTnI appears to have a Raman signature at the approximate wave numbers: 1160 cm^{-1}, 1595 cm^{-1}, 1790 cm^{-1}, and potentially at the approximate wave numbers 1095 cm^{-1}, 1487 cm^{-1}, 1524 cm^{-1}, 1630 cm^{-1}. In order to verify the Raman signature, the PLS weights for both sets of cTnI in BSA and cTnI in serum data, with and without preprocessing, are plotted in Figure 4 to illustrate how they all show a strong correlation with similar wave numbers in Raman spectra. All these spectra reveal the existence of a Raman signature at the following wave numbers: 1160.8 ± 5.4 cm^{-1}; 1596.4 ± 7.3 cm^{-1}; 1790.2 ± 11.1 cm^{-1}.

Discussion

Unique findings and clinical applications

To the best of our knowledge, this is the first study that has successfully characterized and verified the unique Raman signature of mouse cTnI protein in BSA and human blood serum. cTnI is considered to be one of the most specific and widely used cardiac biomarkers [10] for myocardial infarction. The characteristic Raman signature allows for high specificity. Further optimization of our detection apparatus may improve the sensitivity of the cTnI measurement. Advancement in biomedical engineering, coupled with an incentive towards developing non-invasive and expeditious diagnostic devices, has allowed for the

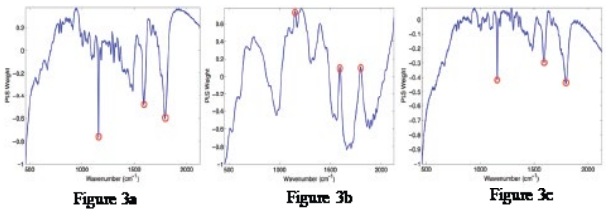

Figure 3a Figure 3b Figure 3c

Figure 3: PLS weights of the most significant, LV for the Raman spectra of cTnI in human blood serum. The red circles from left to right correspond to the wavenumbers 1160 cm^{-1}, 1595 cm^{-1}, 1790 cm^{-1}, respectively. (a) PLS weights of the 2nd LV, for the raw data; (b) PLS weights of the 2nd LV, for the smooth and baseline corrected data; (c) PLS weights of the 1st LV, for the preprocessed data.

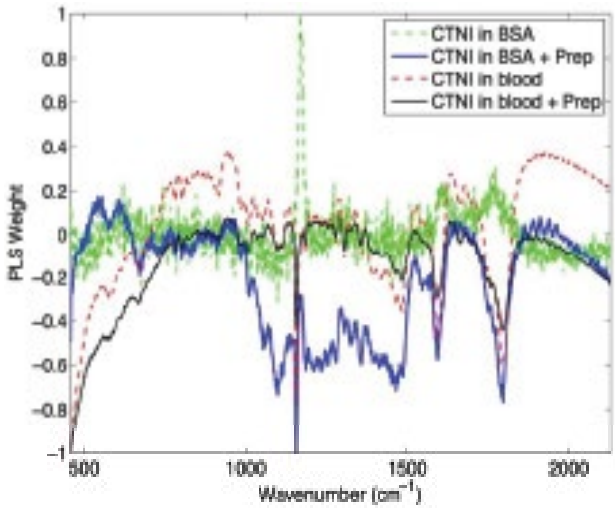

Figure 4: PLS weights for all sets of data, without and with preprocessing.

inception of point-of-care testing (POCT) devices for diabetes mellitus [22], skin cholesterol measurement [23], and some novel cardiac biomarkers [8]. Our findings potentiate technological advancement towards POCT measurement of a very important cardiac biomarker, which can be employed in the outpatient setting and emergency departments especially when the hospitals do not have the capability for prompt laboratory sample processing. A further strength of our technology is its potential applicability to other well-established MI biomarkers such as CK-MB and myoglobin, and recently emerging biomarkers such as ischemia- modified albumin (IMA) [24] or copeptin [25].

Limitation of current available assays

Devices currently implemented in many hospitals for the detection of MI biomarkers have limited accuracies in concentration detection compared to potentially more sensitive technology. The limitation may lead to worse overall outcome for patients presenting with ACS. Furthermore, currently implemented assays for cTnI measurement are not universally standardized, causing variation in the threshold at which a sample is deemed abnormal. This lack of standardization imposes particular disadvantages, as measurement on assays from different manufacturers and at different institutions is not reliably comparable. Currently implemented diagnostic assays require trained personnel for processing in dedicated laboratories. In contrast, our technology proposes an alternative approach to troponin detection, allowing for data acquisition at hospitals and in the field in a matter of only seconds after blood is drawn, without the need for extensively-trained personnel.

Comparison with other POCT approaches

The difficulties of managing a patient with non-specific chest pain, despite employment of a Bayesian approach in order to choose subsequent diagnostic tools, fuels a general trend towards more sensitive and specific assays for the diagnosis of ACS. Similar quantitative and qualitative approaches for the detection of cTnI and other cardiac biomarkers for MI have been previously described in a recent comprehensive systematic review of POCT devices comprising 42 studies [8], with most described modalities principled on immunoassays. Despite these approaches, the review concludes that an optimal POCT for the timely diagnosis of ACS within 6 hours after the onset of symptoms does not yet exist [8]. In fact, recently published studies were deemed generally of suboptimal methodological quality and POCT devices reported an unacceptably high number of false negatives to be considered safe for the diagnosis of ACS [8]. This review, however, does highlight the necessity of novelty and technological evolution of this arena [8]. Compared to contemporary troponin assays [26-29], "high-sensitivity troponin" assays have demonstrated superior sensitivity, negative predictive value, and prognostic implications, but with a suboptimal positive predictive value [30,31].

Qualitative based devices [32] are further inherently limited in that clinical interpretation of cardiac biomarkers are often complicated by an elevation related to non-cardiac causes of chest pain with classic examples pertaining to patients with renal impairment or pulmonary embolism. Moreover, chest pain is a common chief complaint. Its presenting symptoms can vary and correlate with a widely differing diagnoses in individuals with different risk factors. Such diversity in clinical presentations is more common in women and diabetic patients who have other physiological factors, which at times obscure the underlying etiology and delay the vital treatment. A quantitative approach is thus required since the extent of elevation of biomarkers often plays a key role in physicians' management decisions.

Limitations

Inherent limitations impede the practical implementation of our findings. While demonstration of reproducible results in the setting of both BSA as well as human serum is promising and physiologically similar to whole human blood, the identified cTnI signature needs to be corroborated within whole human blood and ultimately *in vivo*. The extremely low physiological concentrations of MI biomarkers and the confounding noise from other ubiquitous molecular structures within the blood create some technological challenges. In addition, despite structural similarities between human and mouse cTnI [12], our findings require corroboration using recombinant human cTnI protein prior to clinical implementation. Lastly, while scientifically feasible, a quantitative apparatus must be engineered, designed and verified for repeatability, accuracy, and specificity in the measurement of troponin concentrations in blood.

Conclusion

In conclusion, we herein present the unique Raman signature of mouse cardiac troponin I protein in Bovine Serum Albumin and Human Blood Serum. Future efforts to optimize this modality for the measurement of cardiac biomarkers could compensate for deficiencies in the currently utilized troponin measurement assay. Ultimately, this finding can assist in optimal diagnosis of patients suspected of presenting with ACS.

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