Enhanced Optical Sensitivity of Polyvinyl Alcohol–Reduced Graphene Oxide Electrospun Nanofiber Coated Etched Fiber Bragg Grating Sensor for Detection of Myoglobin a Cardiac Biomarker

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1. Introduction

Cardiovascular disease (CVD) can be diagnosed in the early stages through primary health care screening of cardiac biomarkers such as myoglobin, creatine kinase (CK), troponin I, and T. Existing CVD diagnostic methods generally rely on expensive classical assays such as immunoproteins-based enzyme-linked immunosorbent assay or paper-based lateral flow assays based on centralized laboratories with test results available only after several hours. The assays are also focused on the diagnosis and postdisease management with the dynamic ranges optimized around the higher concentration ranges, rendering these detection routes useless in the early phase disease screening. Real-time, economically viable, point-of-care test kits at normal temperature and pressure (NTP) for cardiac biomarkers will help screen in remote locations and developing countries to reduce myocardial infarction (MI) risks. Many research groups working toward this goal have developed sensors/techniques based on strain using cantilevers[1]; electrochemical (conductance/resistance)[2,3]; optical methods including fluorescence,[4] colorimetric,[5] UV–Vis,[6] and photonic crystals.[7] Moleculary imprinted polymers (MIPs) are also finding applications with enhanced performance.[8,9] Another technique gaining popularity is polymer nanofibers embedded with nanomaterials adopted in electrochemical and...
chemiresistive\textsuperscript{[10,11]} sensors with increased performance. None of these methods have yet been commercialized, with some methods requiring sophisticated instruments with dedicated personnel to perform tests and thus becoming expensive while others being nonscalable for mass production. A comparison of their performance is given in Table T1, Supporting Information.

After Iadicicco et al. demonstrated the dependence of refractive index (RI) sensitivity on cladding diameter,\textsuperscript{[12]} the applications of etched fiber Bragg grating (eFBG) sensors as RI sensor, pressure sensor, fuel-level sensor, temperature sensor, gas sensor, and biosensor\textsuperscript{[13–20]} are well documented. Even though these sensors have been a research topic for more than 10 years, translating from an idea to a product has not happened due to nonreproducible results, primarily from the coating’s nonuniformity due to their microscale diameter. The methods used to improve eFBG sensors’ repeatability have made them an expensive proposition compared with other commercially available sensors. The proposed polyvinyl alcohol–reduced graphene oxide (PVA–rGO) electrospun coating on the eFBG sensor is a cost-effective solution to obtain highly reproducible results at NTP conditions.

The recent applications of functionalized nanocomposites (nanoparticles, polymers) in biological applications have shown promising results.\textsuperscript{[21–23]} In the present work, a PVA–rGO composite has been electrospun on an eFBG sensor. PVA is a synthetic nonconducting, biocompatible, and biodegradable polymer with hydroxyl groups on its side chains, making them highly hydrophilic.\textsuperscript{[28]} rGO-embedded PVA nanocomposite film has been reported to enhance mechanical property,\textsuperscript{[29]} electrical conductivity,\textsuperscript{[30]} as well as alter the optical conductivity and band structure parameters of PVA,\textsuperscript{[31]} having applications in different sectors.\textsuperscript{[32–34]} The electrospinning method is a cost-effective method to generate nanofibers of required diameter using the electrostatic field principle with simple instrumentation\textsuperscript{[35]} and has found application in different sectors.\textsuperscript{[36,37]} PVA with its unique fiber/film-forming capacity, optical property, immense dielectric strength,\textsuperscript{[38]} and low manufacturing cost can be easily coated using the electrospinning method.\textsuperscript{[19–41]}

Figure 1 shows the proposed scheme to get a uniform coating on the eFBG sensor and an application to study this scheme’s efficacy. Here, the eFBG sensor (Figure 1a) is placed on the customized target (Figure 1b). The shape (cylindrical) and fragility of the eFBG sensor (9 to 13 μm) have made traditional targets (flat sheets or rotating drums), which are typically used in electrospinning, nonviable to obtain a uniform coating. The in situ prepared PVA–rGO solution (Figure 1c) is loaded into the syringe placed in a syringe pump (Figure 1d), and the nanofibers are electrospun onto the sensor using a sandwich protocol. The nanofiber-coated eFBG sensor is removed from the target (Figure 1e) and exposed to glutaraldehyde vapors followed by immersion in tris buffer. The sensor is then incubated in myoglobin (Figure 1f) and exposed to glutaraldehyde vapors followed by immersion in Mb. The hybridization of Mb with DNA is shown in Figure 1f.

2. Fabrication of rGO, PVA, and PVA–rGO eFBG Sensors

The phase mask technique has been adopted for the inscription of gratings in the core of a single-mode (germania doped) optical fiber. The gratings allow the optic fiber to behave as a wavelength-selective filter by reflecting one particular wavelength (Bragg resonant wavelength) \( \lambda_B \) while transmitting the others, on incidence with a broadband light source; the Bragg wavelength is defined by the equation \( \lambda_B = 2n_{\text{eff}} \Delta n \) where \( \Lambda \) is the pitch of grating and \( n_{\text{eff}} \) is the effective RI of \( LP_{01} \) mode.\textsuperscript{[42]} The fiber has a core diameter of 9 μm and a clad of 125 μm. Removal of the clad partially by chemical etch permits the evanescent waves from the core–clad interface to interact with surrounding media, governed by the equation \( \Delta n_0 = \frac{2n_{\text{eff}}(n_{\text{sur}} - n_{\text{cl}})}{n_{\text{cl}}} \) where, \( n_{\text{0}} \) is the fraction of the total power (unperturbed mode) that flows in the clad, \( n_{\text{sur}} \) is the RI of surrounding medium, and \( n_{\text{cl}} \) is the RI of cladding.\textsuperscript{[43]}

Three eFBG sensors (11 ± 0.5 μm) are fabricated in the present work. One sensor is dropped with NH\textsubscript{4}OH: H\textsubscript{2}O\textsubscript{2}: H\textsubscript{2}O
followed by rGO dip (allowed to dry \(\approx 4\) h at room temperature) and finally washed in deionized (DI) water.\(^{[19]}\) The resultant sensor is referred to as the rGO sensor. The second and third sensors are coated with PVA and PVA–rGO nanofibers, respectively, by electrospinning. The nanofiber coating is exposed to glutaraldehyde (a bi aldehyde) vapor, which acts as a crosslinker between individual nanofibers (aldehyde–hydroxyl bond) and reduces porosity. These are referred to as PVA and PVA–rGO sensors.

The PVA–rGO coated sensor’s surface morphology is shown in the scanning electron microscope (SEM) images (Figure 3). The nanofiber coating on the eFBG sensor is shown in Figure 3a. The nanofiber coating post-treatment to glutaraldehyde (Figure 3b) displays a reasonably uniform thickness (\(\approx 1.5\) μm) along the sensor region.

The sensors are subsequently immersed in tris buffer (prepared in 10 mM tris HCl, 150 mM NaCl, 5 mM MgCl\(_2\), pH \(\approx 8\)) and then removed. The Bragg reading is referred to as “before DNA incubation” (\(\lambda_{\text{B, before}}\)). The buffer salts neutralize the negative charge repulsion between rGO and DNA phosphate backbone.\(^{[44]}\) PVA being hydrophilic, swells, and disintegrates, and becomes transparent. The PVA–rGO sensor forms islands in the presence of rGO (white spots) (Figure 3c).

### 3. Optimization of rGO and DNA Concentration for PVA–rGO Sensors

The sensor (described in Section 2) is incubated with 85 μL of anti-Mb DNA (suspended in 1× phosphate-buffered saline

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**Figure 2.** a) Experimental setup showing multiplexed sensor 1 (analyte sensor) and sensor 2 (temperature sensor) held in the 3D-printed sensor holder connected to an interrogator through a patch cord and data analysis with a laptop. A groove is provided to hold the solutions dropped onto sensor 1 through the hole. b) A photograph of the sensor holder.

**Figure 3.** SEM surface morphology of PVA–rGO electrospun nanofibers on eFBG sensor: a) nanofibers on the etched sensor; b) post glutaraldehyde treatment; c) after removal from tris buffer (before DNA incubation). d) Raman spectra of PVA, rGO, and PVA–rGO on eFBG. e) FTIR spectra from PVA, rGO, and PVA–rGO on eFBG.
[PBS] buffer, pH ≈ 7.4) for 50 min (Figure S1, Supporting Information) followed by buffer wash to flush out the unbound DNA. The DNA bases bond to aromatic regions of rGO by π–π stacking.\(^{[45]}\) At the end of incubation, \(\lambda_B\) is measured (\(\lambda_{B\,\text{DNA}}\)), and the Bragg shift (\(\Delta \lambda_B = \lambda_{B\,\text{before}} - \lambda_{B\,\text{DNA}}\)) is calculated. \(\Delta \lambda_B\) is used to measure DNA immobilization on the sensor. Higher values of \(\Delta \lambda_B\) implies better DNA immobilization. The maximum immobilization of DNA on the sensor is dependent on rGO (wt%) and DNA concentrations (ng \(\mu\)L\(^{-1}\)) and is shown in Table 1. Maximum DNA immobilization is equated with maximum Bragg shift which occurs (\(\Delta \lambda_{B\,\text{max}} = 808\) pm) for the combination of 0.01 wt% (rGO) and 12 ng \(\mu\)L\(^{-1}\) (DNA).

The eFGb sensor is temperature-sensitive with the temperature effect inherent in the measured \(\lambda_B\), thus making its measurement necessary. The temperature response at experimental conditions is determined by multiplexing a second PVA–rGO coated sensor (sensor 2, Figure 2) to sensor 1 (primary sensor), but without further incubations/immersions as sensor 1, and measuring \(\lambda_B\).

### 4. Results and Discussion

#### 4.1. Characterization

Electron dispersive spectroscopy (EDS) analysis is used to determine the elemental composition of PVA–rGO sensors. The atomic % of carbon (C), oxygen (O), and silicon (Si) on the white spots (of Figure 3c) are 26, 56, and 17, respectively, whereas that of the black background are 34, 43, and 21, respectively. There is a decrease in the C content and an increase in the white spots’ O content. The actual reason for this needs an understanding of the chemical structure.

Raman spectroscopy has been conducted (Figure 3d) for rGO, PVA, and PVA–rGO sensors. PVA has an intense peak at 2912 cm\(^{-1}\), ascribed to \(\text{CH}_2\) stretching vibration.\(^{[46]}\) rGO has characteristic peaks at 1358 cm\(^{-1}\) (D) and 1594 cm\(^{-1}\) (G) attributed to induced Raman mode and symmetry allowed tangential mode, respectively. Both these peaks are seen in the PVA–rGO sensor. The increase in \(I_D/I_G\) intensity ratio from 1.1 (rGO) to 1.2 (PVA–rGO) can be explained as the generation of sp\(^2\) carbon domains with a smaller average size.

Fourier transform infrared (FTIR) spectroscopy (Figure 3e) has been performed to study the chemical bonds of PVA–rGO, PVA, and rGO. Both PVA and rGO display a characteristic peak at 1723 cm\(^{-1}\) (C=O), an indicator of residual oxygen-containing groups. The band between 2840 to 3000 cm\(^{-1}\) (C–H) appears due to glutaraldehyde. The broadband between 3550 to 3200 cm\(^{-1}\) (O–H) in PVA and PVA–rGO is associated with the existence of strong inter and intramolecular hydrogen bonds.\(^{[47]}\) The reduction in this peak intensity from PVA to PVA–rGO is attributed to interfacial interaction between PVA and rGO. Similarly, the decrease in intensity in 1150 to 1085 cm\(^{-1}\) (C–O) stretching mode is related to removing oxygen-containing functional groups and forming strong hydrogen bonds between PVA and rGO.

Raman and FTIR results indicate that embedding PVA with rGO and post-treatment with glutaraldehyde results in strong interfacial interaction between PVA and rGO.

#### 4.2. Case Study: Myoglobin Sensing

The measured \(\lambda_B\) up to DNA immobilization is shown in Figure 4a for the PVA–rGO sensor. All the measurements are made at NTP conditions. Each of the DNA immobilized sensor (rGO, PVA, and PVA–rGO) is initially drop cast with fixed volume (85 \(\mu\)L) of PBS buffer without Mb (0 g mL\(^{-1}\)) accompanied with Bragg wavelength measurement (\(\lambda_{B\,\text{Ref}}\)). This step is followed by incubation in the lowest concentration of Mb aliquot (prepared in PBS buffer) for a total of 10 min (this ensures that the measured \(\lambda_B\) curve becomes reasonably flat). These steps are repeated for all the Mb concentrations (10 ag mL\(^{-1}\) up to 100 \(\mu\)g mL\(^{-1}\)). After a dip in each concentration, the sensor is washed in PBS buffer to flush out the unbound molecules before adding the next higher concentration.

Figure 4b shows the plot of \(\lambda_B\) versus time for the PVA–rGO sensor. The limit of detection (LOD) of the sensor depends on the signal to noise (S/N) ratio at experimental conditions. The S/N is determined by the interrogator’s wavelength repeatability (1 pm) and environmental noise. As the experiments are conducted at NTP, the standard deviation (\(\sigma = 5.7\) pm) of the sensor signal (0 g mL\(^{-1}\)). Figure 4b is used for the determination of noise margin (Figure S2, Supporting Information). Chiavaioli et al.\(^{[48]}\) have stated that a sensor’s LOD can be considered as \(3\sigma\) (17.1 pm), which is 100 ag mL\(^{-1}\) (\(\Delta \lambda_B = 64\) pm) and is well within the clinical detection limit of Mb (90 ng mL\(^{-1}\)). In the event of Mb, Mb (in human blood) increases above the normal value (0–90 ng mL\(^{-1}\)) within the first 2 h, reaches a peak (≈600 ng mL\(^{-1}\)) between 8 and 12 h, and returns to normal within 24 h. The sensor response is seen to lie well within the required clinical range.

The differences between \(\lambda_B\) and \(\lambda_{B\,\text{Ref}}\) (\(\Delta \lambda_B\)) for all the Mb concentrations are calculated. The Mb linear plots for PVA–rGO (1 fg mL\(^{-1}\) up to 1 \(\mu\)g mL\(^{-1}\)) and rGO sensor (1 fg mL\(^{-1}\) up to 100 \(\mu\)g mL\(^{-1}\)) are shown in Figure 4c with sensitivities of 286 pm 10\(^{-1}\) g mL\(^{-1}\) and 12 pm 10\(^{-1}\) g mL\(^{-1}\) respectively. The PVA sensor did not show any measurable response. Furthermore, an increase in Mb concentration causes a decrease in \(\lambda_B\) for the rGO sensor, whereas it increases for the PVA–rGO sensor.
The reason for this can be explained as follows: the DNA immobilized on the sensor surface has a net negative charge with a fixed electron (\(e^-\)) transfer rate between DNA and buffer. The hybridization of Mb (heme group + globin protein) with DNA is accomplished by reduction of iron (center atom of heme group) from ferric to ferrous (Fe\(^{3+}\) \(\leftrightarrow\) Fe\(^{2+}\)) with a net decrease in \(\varepsilon\) transfer rate. The reduction will cause a decrease in the bulk dielectric constant (\(\varepsilon\)) with a consequent decrease in RI (\(n\)) of the Mb solution (\(n \propto \varepsilon^{1/2}\)). The higher Mb concentration will increase hybridization with a further decrease in RI of the solution and lower values of \(\lambda_B\) for rGO sensor and higher values of \(\lambda_B\) for PVA–rGO sensors.

The higher value of \(\lambda_B\) for lower RI indicates a PVA–rGO sensor with a negative RI sensitivity. The RI experiment, which includes the sensor to be dipped in each concentration (85 \(\mu\)L) of the prepared sucrose solution (Section 7.1) for 10 min (accompanied by \(\lambda_B\) measurement) followed by DI wash, confirms this hypothesis. Figure 4d shows the \(\lambda_B\) plots for sucrose solutions of different RI for both rGO and PVA–rGO sensors. A linear regression fit for the plots gives a downshift of 1.45 nm for every one unit decrease in RI for rGO sensor and an upshift of 6.9 nm in \(\lambda_B\) for every one unit decrease in RI for PVA–rGO sensor.

The reproducibility in the sensor performance is established by repeating the Mb experiment on three similarly prepared DNA immobilized PVA–rGO coated sensors (Sections 2 and 4.2). The mean and \(\sigma\) at each concentration are calculated. The \(\sigma\) is shown as the error bar (Figure 4c) and gives a standard error of \(\pm 2.3\%\) (10 pg mL\(^{-1}\)).

The sensor response to temperature changes at experimental conditions needs to be determined, as stated earlier. The temperature sensor has a standard deviation of 1.73 pm (Figure S3, Supporting Information), which lies well within the sensor’s noise margin (17 pm) and makes Mb sensor response (Figure 4b) independent of temperature effects.

4.3. Enhancement of PVA–rGO Sensor Response

The PVA–rGO sensor has increased by \(\approx 4\) times in the RI sensitivity than the rGO dip sensor. This increase has led to an increase in the LOD (\(\approx 90\%\)) (LOD of rGO sensor is 1 fg mL\(^{-1}\)) and a phenomenal increase in Mb sensitivity (\(\approx 24\) times) and linear range (\(\approx 10\) K times). The explanation for this enhancement can be attributed to two factors: one is the strong interfacial bond between PVA and rGO (as determined by the FTIR and Raman results), and the second is the uniformity of the PVA–rGO nanofiber coating (as determined by SEM results). The electrospinning of nanofibers (PVA–rGO) using the customized
target and sandwich arrangement provides the initial uniformity in a coat over the eFBG sensor. Postprocessing of the nanofibers with glutaraldehyde makes the PVA matrix a strong adhesive for rGO entrapment on the sensor surface. The rGO is responsible for DNA–Mb hybridization. The thickness of the PVA–rGO nanofiber coating can be precisely controlled (by fine control of the electrospinning parameters) to obtain reproducible sensors. The PVA–rGO sensor performance for Mb sensing is better than the other techniques listed to date (Table T1, Supporting Information), showing the least LOD and highest dynamic range.

4.4. Cross sensitivity and Stability of PVA–rGO Sensor

The cross-sensitivity of the PVA–rGO sensor has been determined by conducting experiments similar to Mb sensing (Section 4.2) with aliquots (10 pg mL\(^{-1}\) to 100 μg mL\(^{-1}\)) of other proteins commonly present in human plasma (hemoglobin and hematin) and bovine serum albumin (BSA), a protein structurally different from Mb). The Δ\(A_B\) has been depicted as the height in Figure 4e, displaying a very low cross-sensitivity of the sensor for other analytes.

The long-term stability of the PVA–rGO sensor has also been determined. One of the sensors used for Mb sensing (Section 4.2) (last measured value is Δ\(A_B, 100_μ\) for 100 μg mL\(^{-1}\) Mb) is immersed (after 1 month of the initial experiment) in 100μg mL\(^{-1}\) (85 μL) of Mb for 10 min at NTP conditions and is accompanied by Δ\(A_B\) (Δ\(A_B, 100_μ\)) measurement. The error is calculated as (Δ\(A_B, 100_μ\) − Δ\(A_B, 100_μ\))/Δ\(A_B, 100_μ\). The experiment is repeated for the same sensor in 3, 6, 9, and 12 months. The sensor shows a maximum error of <0.5% after 12 months.

5. Conclusion

PVA–rGO nanofibers have been coated uniformly with the required thickness on the eFBG sensor using an electrospinning technique with a customized target and sandwich arrangement. The electrospinning parameters have been optimized to achieve low sample volume (<0.1 mL) and spinning time (~8 min). Postprocessing with glutaraldehyde vapors has resulted in PVA–rGO nanofiber coating can be precisely controlled (by fine control of the electrospinning parameters) to obtain reproducible sensors. The PVA–rGO sensor performance for Mb sensing is better than the other techniques listed to date (Table T1, Supporting Information), showing the least LOD and highest dynamic range.

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Materials and Methods: 5'–ATCCAGGTACCACGCA–3' and 5'-biotin–ACTAAGCCACCGGTCCA–3' are the sequences of primers (S5, Supporting Information). Purified DNA library of 5'-ATCCAGGTACCACGCA (N45) TGCCACCGCAGTCTAC-3', PVA (powder) (MQ 200), hydrofluoric acid (HF) (40%), hemoglobin (MQ 200), hematin (MQ 200), BSA (MQ 200), PBS (10%), sucrose (MQ 100), and graphite flakes (MQ 100) were procured from Sigma Aldrich. All other reagents and solvents were used without purification.

The Mb stock solution of 1 mg mL\(^{-1}\) was prepared using PBS (1×, pH ≈ 7.4) from dehydrated 10 mg mL\(^{-1}\) (laboratory synthesized) Mb. Aliquots of Mb ranging from 100 μg mL\(^{-1}\) to 10 ag mL\(^{-1}\) (in steps of tenfold decrease) were prepared using PBS buffer for dilution.

Sucrose concentrations of 0, 6, 10, 20, 30, 40, and 50% (which had a predefined RI) were prepared using DI as the solute.

Drop Cast (Dip/Immerse) Experimental Setup: The 3D-printed sensor holder included four separate pieces (two bases and two plates) fitted together (Figure 2). The analyte sensor (sensor 1) (3 mm) was multiplexed with the temperature sensor (sensor 2), and the combined sensors (with extra fiber length) were positioned between the two plates such that sensor 1 was accessible through a hole (4 mm diameter) provided in both the plates whereas sensor 2 was inaccessible. The liquids were pipetted through the hole onto sensor 1. A base with a groove/well (4 mm diameter, 1 mm depth) was placed below the hole to hold the liquids and a second base for support. The interrogator (Micron Optics SM 130) had a tunable laser source (1510 to 1590 nm) with an inbuilt receiver and spectrum analyzer. The interrogator was connected to the sensor (through a patch cord) and laptop to capture and save Δ\(A_B\).

In situ Preparation and Electrospinning Process: PVA–rGO sensor required lab prepared rGO (prepared using green synthesis method starting from graphene oxide)\(^{100}\) of required wt% to be dispersed in DI water (2%) and sonicated (1 h) and was transferred into a beaker along with remaining DI (98%) and kept on a hot plate (70 °C). The PVA (12 wt%) was added in small amounts with continuous stirring (4 h) followed by mechanical stirring (8 h, without heat). The prepared PVA–rGO solution (Figure 1d) was loaded into a syringe (1 mL) and held in a syringe pump (Figure 1d) with the flow rate set at 280 μL h\(^{-1}\). The needle (0.4 mm diameter) was connected to the anode of a high voltage supply and the aluminum (Al) sheet (foil) (prepared as per 3D-printed customized plastic mold) to the cathode (Figure 1b). On applying a high voltage (13 kV) between the anode and cathode, the nanofiber layer was formed and collected (4 min) across the Al bridge. The eFBG sensor was placed perpendicular to this nanofiber layer and coated again (4 min). The result was an eFBG sensor sandwiched between two nanofiber layers (with <0.1 mL solution). See ST6, Supporting Information, for optimization of electrospinning parameters.

PVA sensor required the PVA (12 wt%) to be added slowly to DI water and stirred continuously for 4 h by maintaining the temperature at 70 °C, after which it was stirred for 8 h at room temperature.

Raman and FTIR Spectra: Raman spectra were recorded (HORIBA Scientific instrument) using 532 nm laser excitation with 100× objective and averaging to improve the S/N ratio. The FTIR experiments had been performed (Perkinelmer, Frontier) to capture samples’ spectra in 4000 to 650 cm\(^{-1}\) range with 4 cm\(^{-1}\) resolution using ATR (Attenuated total reflection) mode. The average (32) of collected spectra was calculated to improve the S/N ratio.

UV Spectrophotometer Studies: The DNA had a maximum absorbance at 260 nm, and the concentration of DNA solutions (IN and OUT of Table 1) was measured using microvolume (2 μL) mode of DeNovix DS-11 FX spectrophotometer. PBS (1×) buffer was used for blank. “IN” is the concentration of the prepared DNA solution. “OUT” is the collected DNA
solution after incubation on the sensor (i.e., the unattached [mobile] DNA concentration). Percentage immobilization is calculated as (IN − OUT)/IN × 100.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
Research data are not shared.

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