Current Strategies with Sensing Technologies to Eliminate Stress Cardiomyopathy

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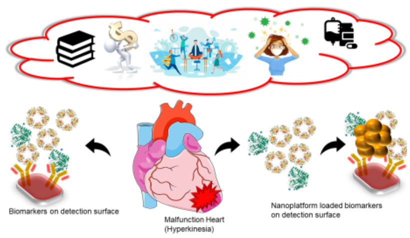
Abstract

Stress cardiomyopathy refers weakening of heart muscle due to the continuous stress. Generally, the severe status of stress cardiomyopathy has been revealed after damaging the muscles and measured by the physical changes in the heart system. To overcome this issue, biosensor can be used, which could eliminate the late identification stress cardiomyopathy. With biosensors, different stress markers such as, epinephrine, dopamine, catecholamine, α-amylase, norepinephrine, serotonin and cortisol have been identified by a wide range of developments. These biosensors are available from laboratory to industry at the ranges of nano- to macro-devices. To merge with the identification of stress cardiomyopathy, the above strategies might be utilized properly and can aid to reduce the stress-related problems. This overview, gleaned the currently available biosensing methods and the associated biomarkers, at various stages of the developments and implementations of stress cardiomyopathy.

Graphical Abstract



Keywords: Cardiomyopathy; Stress biomarker; Early diagnosis; Cardiac diseases

1. Introduction

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In 1980, Cebelin and Hirsch introduced a term ‘stress cardiomyopathy’, an evanescent apical ballooning [1] or a mimic of acute myocardial infraction based on the analytical discoveries on autopsy and patients who died due to the physical attack without any internal bleeding. Stress cardiomyopathy also known as ‘Tokotsubo’ cardiomyopathy (TTC) and this term emerged from Japan by referring to the shape of Japanese octopus trap, which resembles apical ballooning [2]. This name becomes more popular among Japanese cardiologist in 1990 while nowadays they describe this condition as ‘tokotsubo’ universally. This syndrome is frequently evoked in distinguishable physical and emotional stressor for example accident cases, unexpected loss of loved one, medical operation procedure and risk disease. This is due to acute heart failure featured by the reversible impairment in myocardial tissue. The occurrence of this syndrome is predominant with postmenopausal women. It has a prevalence of 2% among all emergency patients for acute coronary syndrome and about 10% of postmenopausal females [3]. Four different patterns of left ventricular malfunction have been described in TTC as illustrated in Figure 1, but the riskiest is apical ballooning characterized by akinesia or dyskinesia of the left ventricular apex and hyperkinesia of basal parts. The significant symptoms of TTC are highly engaged to acute coronary syndrome and/or acute myocardial infraction for an instance palpitation, chest pain, dyspnea or syncope. Several clinical molecules are responsible for the direct symptoms of TTC like epinephrine [4], dopamine [5], catecholamine [6], norepinephrine [7] serotonin, cortisol, α-Amylase and neuropeptide Y(NPY). Regardless of past cases for stress cardiomyopathy, currently due to the global pandemic COVID-19 the statics for this syndrome elevates drastically [8]. The universal effect by the virus has been associated with stress and anxiety worldwide. Recently, quite high number of cases were reported by clinicians regarding TTC syndrome due to the financial circumstances, less interaction with outsiders, tight physical distancing rules, and also compulsory quarantine as a result of COVID-19 pandemic. A study was conducted [9] to justify that an individuals without the history of cardiovascular disease affected were recovered from this syndrome in this severe situation of COVID-19. Though, early kick-start step should be implemented in order to thoroughly drain out the syndrome among the affected people. Robust, reliable, quantitative detection of biomarkers with super low concentration is a great and important clinical setting. Therefore, emergence of biosensor in medical department plays a crucial role associating with detecting biomarkers in order to deliver a great outcome in short period of time.

Biosensor, an analytical device able to detect ultralow concentration of clinical molecules with nanomaterial engineered surface [10]. However, biosensor is not only to identify the existence and amount of the analytes but also to explore some other phenomena such as drug delivery in cells, cell mechanics and cell physiology [11]. Usually, bioanalytical devices are developed based on the target and electrical transduction system in order to obtain a quantifiable signal with super resolution [12]. In addition, a device must be capable to differentiate between the target and non-specific biomolecules in the detection solution. The performance of the designed biosensor generally tested in terms of sensitivity, selectivity, limit of detection, specificity at the desired range of detection [13]. Nanomaterial is a hallmark in biosensor application owing to its outstanding characteristics like increase the surface to volume ratio, biocompatible, electrical conductivity and high catalytic activity [14]. Nanomaterial engineered surface able to adsorb more targets on its surface and capable to detect more analytes compared to non-engineered surface. This phenomenon helps to increase the sensitivity of the sensing system [15]. While to achieve the selectivity of the detection, surface functionalization procedure needs to be appropriately supervised by loading more targets on the nanomaterial engineered sensor surface. The conjugation between targets and nanomaterial can be covalent binding or non-covalent binding [16]. The stability of the sensor can be obtained by implementing a good surface chemistry between biomolecules and also the sensor surface [17]. Hence, due to an elevating number of stress cardiomyopathy cases associating with global pandemic, presently biosensor capable to decline the amount new cases evolving every day. The integration of nanomaterial could help by increasing the sensing performance [18]. This review mainly about the key role played by nanomaterial and immobilization hierarchy as an ideal platform to diagnose this syndrome. Recently, new technologies were also integrated into biosensor applications to enhance the detection system. Several of these procedures have been narrated in this overview.

Highlights

Stress cardiomyopathy refers weakening of heart muscle in the heart system. Biosensor could eliminate the late identification by analyzing different stress markers. Biosensors are available from laboratory to industry at the ranges of nano- to macro-devices and this review gleaned the currently available biosensing methods and the associated biomarkers, at various stages of the developments and implementations.

2. Potential Biomarker for Stress Cardiomyopathy

Diagnosis for TTC can be done based on symptoms, biomarkers, electrocardiogram, coronary angiogram and noninvasive detection [19]. Key goal of this review is to overview the importants of biosensor in utilizing stress biomarker to handle the stated life-threatening syndrome now and later. Particularly, specific and sensitive detection systems are highly significant and demanded for disease diagnosis. Thus, by conducting early diagnosis for TTC could able to increase the recovery and survival rate [20]. Though, the clinical biomolecules level usually in low abundance at the early stage of disease prognosis. The term clinical biomolecules refers biomarker to confirm the emergence of disease and the concentration of the biomarkers indicates the level of the disease progression [4]. Biomarker is a clinical biomolecule usually utilized in biosensing applications with ultralow concentration to limit the cost of the sensing system. There are several biomarkers are associated with TTC syndrome such as epinephrine, dopamine, catecholamine, α-Amylase, norepinephrine, serotonin and cortisol [21]. These biomarkers are usually elevating in the concentration to trigger the TTC syndrome. Biomarkers in TTC syndrome reflects the hormone release once the body response to the extreme stress level. Endocrine and nervous systems are mainly responsible to plush out the hormones to mediate its effect [22]. Endocrine system releases the hormones into the bloodstream and the hormones and travel until they reach their target. Two types of hormones are available; hydrophilic and hydrophobic hormones. Hydrophilic hormones can solely travel in blood vessels while hydrophobic hormones have to attain the assist from carrier protein and moved into cell nucleus to bind with intracellular receptors [23]. Nervous system comprises of central nervous and peripheral systems. These systems usually release the neurotransmitters [24] to deliver nerve signals from neuron to the specific target like muscle, gland cell or another neuron. Most common biomarkers of TTC syndrome are serotonin collected from patient's blood sample, dopamine from urine sample, cortisol from sweat and α-amylase from saliva. Brief illustration on how the biomarkers are released from stressor body system via endocrine and nervous system is shown in Figure 2. Therefore, released hormone and neurotransmitters biomarker plays an ideal role in diagnosing TC symptoms.

3. Macro to Nanosensor: Laboratory to Industry

Decade earlier, several methods were practiced to diagnosis stress biomarkers like, chemiluminescence, high performance liquid chromatography, capillary electrophoresis, fluorescence and electrochemical methods [25,26]. Yet, conventional methods are laborious, expensive, high amount of sample needed and also complicated. Thus, quick and sensitive method is much needed to diagnosis this TTC syndrome due to the increment in death toll day-after-day. Additionally, concerning about the global pandemic has no end and difficult to reach zero cases until now. The steepness of the death curve still increasing universally at the specific moment in the outbreak. So, government had announced strict standard operating procedure (SOP) to bend the death curve globally and associating with new normal, people involved in extreme stress living lifestyle. Thus, TTC syndrome cases also elevates drastically due to this new norm. In order to lower the amount cases into controllable quantity early detection system must be worked out to decline the progression of the disease. Therefore, implementation of new technologies into industries recently attracts the cardiologist and physical clinicians with outstanding key features like low-cost, easier, biocompatible, robust and rapid outcome. The birth of nanosensor in recent research industries with nanomaterial engineered surface [27] for detection was an eye-catchy for medical departments to diagnose TTC syndrome as quick as possible. The emergence of biosensor was shown via timeline progress in Figure 3.

4. Nano-platform in sensing strategies for Cardiomyopathy

Updated nanotechnology comprises of nanobiology, information technology and devices display unflinching growth in many fields, like food technology, clinical diagnosis and environmental monitoring [28]. Herein, current review emphasizes on the integration of novel functional nanobiology, which incorporates various fields like engineering, physics, electrical and electronic into other science areas such as biology, biotechnology and chemistry for the detection of TTC syndrome [29]. Rapidly growing nano-platform is opening the door for the current biomedical and acute human health risk for the explosive development of novel nanosensor, which is repetitively in pursuit for high sensitivity, specificity and low limit of detection [30] (Figure 4).

4.1. Nanomaterial

Thanks to metal nanomaterials for revealing good features in medical diagnostics address to its super electrical transduction, high surface-to-volume-ratio and adsorption properties and the size of nanomaterial approximately to be 1-100 nm. This vital feature strongly supports the advantageous of nanomaterial because lesser the size of a material the higher the contribution for specific purpose [31,32]. For example, graphene in the detection of salivary biomarker associating TC syndrome. As the existing reviews reported that graphene is the good candidate for the electrochemical biosensor detection. Graphene has converted the investigators attention towards their outstanding electrical and mechanical properties [33]. Graphene also rich in antimicrobial properties as reported in many journals. Hence, graphene was utilized widely in rapidly growing research areas to find viable solutions for the early detection of life-threatening disease like TC syndrome. A study was conducted [34] using graphene as modification material on the sensing surface to detect epinephrine. A carbon paste electrode was covered with graphene nanosheets and inserted into detection solution and it shows virtuous electrocatalytic effect. The analytical performance displays excellent outcomes; detection limit was 5×10^{-8} M. The results obtained justify that the developed sensor is portable to detect epinephrine with high sensitivity, specificity and stability. Other nanomaterial like carbon also contributes broad beneficial for TC syndrome detection. Carbon capable to increase the momentum of electron, lower the biofouling effect, stable and biocompatible to be utilized in detection system [35].

4.1.1. Nanoparticles

Unrecognizable by human naked eye, nanoparticles are ultrafine particle that in size range between 1 and 100 nm. Mentioned ultrafine particles exhibit a large attention in biosensor pool by displaying remarkable optical and physical properties [36]. Greatly it also plays crucial role in diagnosing TTC syndrome by owing high surface to volume ratio to ease the binding event between target and analyte creating higher sensitivity, specificity and stability of the developed detection system [37]. Several studies were conducted to justify that nanoparticles are paving the way to develop outstanding system for early detection in conjunction to decline the mortality rate. For example, a sensor was manufactured to detect serotonin by using gamma ray irradiated tungsten trioxide (GI-WO_3) nanoparticles. Developed device shows outstanding performance by revealing 1.42 nM as the detection limit [38]. Further work for the serotonin detection was carried out using silver selenide (Ag_2Se) nanoparticles [39]. Modified sensor using Ag_2Se nanoparticles shows satisfactory results like 29.6 nM as detection limit, good stability, sensitivity and capable to implement in real human sample testing.

4.2. Nanostructures

Combination of active metal nanomaterial with unique morphology can be term as nanostructures. Combined nanomaterial to form unique nanostructures are capable of enhancing the electrocatalytic activities and electron movements between the sensing surface and also immobilized biomolecules. Nanodiamond, nanocrystal, nanocage, nanostar and nanoribbon are the examples of different nanostructures available in research market for the efficient and rapid sensing system in clinical diagnosis. An efficient nanosensor was developed to detect epinephrine [40] using tetrahexahedral (THH) Au-Pd nanocrystal to modify the sensing area. The detection limit was 0.0012 μM with 0.001 to 1000 μM linear detection range. Results obtained strongly justify that engineered nanosensor is highly suitable to diagnosis epinephrine in real clinical samples. Another recent study demonstrates the uniqueness of nanostructures in diagnosing TTC syndrome. Chevron-like graphene nanoribbons (GNR) [41] was synthesized using chemical method to hybridize on the glassy carbon electrode. This modification was carried out to accelerate the sensitivity and specificity of the system. The limit of detection was 2.1×10^{-6} M and the linear range was from 6.4×10^{-6} to 1.0×10^{-4}M. Based on the analytical performance outcomes, resulting sensor can be undeniably utilized to test epinephrin in real human samples.

5. Nanohybrids for sensor development

Key features of nanohybrids also have opened up a gate of chances for robust and unique sensor development in mental healthcare management [42]. Nanohybrids owes more than a few advantageous like capability of enhancing the sensing sensitivity, accelerate the ionic and electron mobility with greater kinetics and increase the capturing event between target and analytes [43]. Few researches were carried out using nanohybrids as sensing performance boosting material to detect stress biomarkers.

5.1. Integration of gold nanostructures

An electrochemical detection system was designed with the integration of tetrahexahedral gold-palladium (TTH Au-Pd) core shell nanocrystals associating with reduced graphene oxide to detect epinephrin. Good electrocatalytic properties of TTH Au-Pd nanocrystals is essential for the detection purpose of epinephrine [40]. The electrochemical study was carried out to justify the synthetization of TTH Au-Pd nanocrystals on the sensing surface. Revealed results shows lower limit of detection at 0.0012 μM and the concentration linearity range at 0.001 to 1000 μM together with superior sensitivity, selectivity and stability. Designed sensor capable to be utilized in the testing of clinical samples due to good stability. Gold nanoelectrode platform was implemented for the detection of dopamine [44]. This electrode was fabricated using laser interference lithography and electrochemical deposition. The fabricated electrode classified as best electrode among other fabricated electrode for electrochemical dopamine detection via performed analytical performance. The detection limit was 5.83 μM with the linear range from 1 to 100 μM. This study confirms the usage of fabricated gold nanoelectrode for multiple applications like toxicity monitoring in drugs, chemicals and nanomaterial on human nerve cells. Sangamithirai et al. [45] reported the detection of dopamine via poly(o-methoxyaniline)-gold (POMA-Au) nanocomposites. An electrochemical system was designed by integrating POMA-Au nanocomposites to enhance the sensitivity of the sensing system. The fitness of nanocomposites for the dopamine detection was tested by performing analytical test. The outcomes were great as the linear regression was between 10 to 300 μM and 0.5 to 900 μM, while the detection limit was 0.062 μM and 0.09 μM correspondingly. Oxidative stress biomarker, 3-nitrotyrosine (3NT) is an appropriate biomarker for nitrosative stress linked with many chronic diseases. A novel hybrid nanomaterial was synthesized by integrating zeolitic imidazolate framework into gold nanoclusters to act as modifier on sensing platform [46]. This research capable to expose good result by hybridizing synthesized hybrid nanomaterial; limit of detection (1.8 nM at a signal to noise ratio of 3) and linear concentration range between 5 to 200 nM.

5.2. Integration of graphene nanostructures

Graphene is a notable material among others in research world for biosensing purpose till now due to a wide usage for clinical disease diagnostics and owing to its extraordinary optical and physical properties. Portable detection of dopamine was carried out using graphene as a sensing platform for the construction of electrochemically active biosensor [47]. High technological designed sensor works out greatly by proposing a linear range (5 μM-10 mM) and 200 nM as the limit of detection. Another research was published by practicing green technology to synthesis gold nanocrystals and capped with graphene quantum dots for sensing enhancement purpose. This configuration was physically characterized for the detection of epinephrine and dopamine [48]. The incorporation of synthesized nanohybrids have drawn a largest outcome in this work due to designed nanohybrids unique characteristics like good electrocatalytic activity, stability and conductivity. Associating with superior features of the nanohybrids, detection limits for dopamine and epinephrine were 5 and 10 nM, correspondingly. Proposed sensor is highly selective in the presence of other biomolecules which is appropriate for real application. Recent study presented an electrochemical nanosensor modified with gold nano/micro islands fused graphene nanosheets [49]. This nanohybrid holds pivotal role by boosting the sensing sensitivity for accurate outcome in the determination of dopamine. The detection limit was 1.13 nM at concentration linearity between 1 nM and 100 μM. Thus, obtained results suggest implementing the proposed design for real human samples testing.

5.3. Digital diagnostics in relieving stress cardiomyopathy

According to U.S. National Library of Medicine, stress is defined as body's response towards the challenge or demand. Prolonged stress to an individual can lead to the mental health disorder. Thus, early detection for stress disorder is utmost important to prevent from highly risk cardiovascular disease, which may cause direct mortality. Besides, in human daily life stressful situation compulsorily encountered due to high risk occupation. This situation able to paving the way to depression and anxiety. Since, a lot of complication is rising because of stress, expert physicians and cardiologist turn their attentions to find viable solutions by deeply investigates the associating obstacles in digital diagnostics. Several technologies were practiced to diagnosis the stress disorder yet the count of mortality still remaining the same. Currently upgraded technical system together with the role of nanotechnology plays significant role in diagnosis TTC syndrome. Wearable sensor attracts the cardiologist nowadays in diagnosing the syndrome in quick and easy ways. A study was conducted by presenting large-scale wearable data to study the digital characteristics for everyday stress observation [50]. A bunch of people were investigated to collect several information-like subjects' demographics, baseline psychological information, and five consecutive days of free-living physiological and contextual measurements by utilizing wearable device and smartphones. While, collected data represents the associations between wearable physiological signals and self-reported daily-life stress. Montesinos et al. [51] have proposed off-the-shelf wearable sensor with multi modal machine learning technique by incorporating the collected data in wearable sensors or some biosignals to detect acute stress syndrome. Three main stages were proposed in this work, firstly signal acquisition, data processing and finally model learning and the evaluation. An outstanding system was designed using proposed technique to detect stress using combination of several physiological signals from two different wearable sensors. A hassle-free system with the integration of graphene-based wireless sensing method was designed to detect cortisol from human sweat [52]. In this study microfluidic three working electrode system modified with silver, silver chloride modified reference electrode and graphene modified counter electrode were utilized to design the system for concurrent multichannel analysis. Hence, developed digital analysis system reveals an outstanding outcome via presenting good interconnection between circulating hormones, the diurnal cycle, and the dynamic stress-response profile. Proposed approach may proceed for the next level of technology improvement in health management and personalized human performance. The overview of digital diagnostics (Figure 5).

6. Current insights challenges

Albeit, major drawbacks amongst the available biosensing devices are high cost, least accuracy and sensitivity. Hence, the huge challenge in research institutes and industries for human healthcare system is development of miniatured biodevice to carry out in situ diagnosis and treatment. Pointing towards recent technologies digital diagnostic method was widely used for example wearable tear sensor, saliva sensor, wound sensor, ISF sensor, eatable sensor and wearable or implantable blood biosensor. By implementing those sensors in healthcare system, many challenges were addressed like less accuracy, security and privacy, high expenses, power usage, and also compatibility testing. Development of digital biosensor must be highly accurate in order to gain better result. This is one of the medical departments demand towards industries and research institutes to save patients life at the early stage. Herein biosensing application, accurate means specific biomarker must be utilized to diagnose particular diseases to avoid non-specific detection means least accurate outcome. In this case, highly specific biomarker[53] needed to diagnosis the disease. CA-125 is the well-known antigen for ovarian cancer for past three decades but not practical for ovarian cancer detection because at an early stage, the antigen is present only at rising levels in approximately half of patients, while it is present in 92% of patients with a fourth stage. This complication confuses the medical department to confirm and diagnosis the disease. Thus, this challenge triggers the research institutes to find and characterize specific biomarker for ovarian cancer. HE4 is the utmost biomarker which will elevates at two thirds of early and late stage of ovarian cancer patients. Secondly, high expenses to build an outstanding biosensor also become a challenge of the biosensing field. For examples, high-tech digital machine to develop a sensor is much needed for good outcome because low-cost product may lead to less accurate outcome[54]. Thirdly, wide knowledge in biology and electronics are highly recommended to operates sensing instrumentations. Well-trained personnel with good hands-on skill are often required by research institutes to perform their work. This limitation conjugates with educational institutes who are responsible to train their students by conducting practical session implementing hands-on skill which are originally far from each other. In biosensing application, validation and characterization method are significant in order deliver accurate and solid outcome to patients[55]. The instruments involved in validation and characterization method like AFM, SEM, HPM, XRD and FTIR are high in cost which limits their service mainly to laboratory testing. Concerning about the challenges, recent strategy of processing the biosensing information has changed the biosensor. The artificial intelligence (AI) and wearable sensor enables great acquisition of patient’s data together with observation of patient’s fitness, health and surroundings. It composed of three main elements: information collection, signal conversion and AI-data processing. Information collector responsible to collect and monitor wearers’ via physically, chemically, biologically or environmentally. While signal convertor able to convert info received from information collector into electrical signal with well-defined sensitivity. AI-data processor with the combination IoT able to improve the existing digital diagnostic system and helps to meet the healthcare needs and enable in rapid development of intelligent biosensors. Hence, fast growing technology with the help of nanotechnology able to develop an ideal point-of-care diagnosis at the early stage of disease progression and avoid epidemics.

6. Conclusions and Future Perspectives

Written review endeavour to accumulate recent research approaches available in research bank towards determination of stress related biomarkers with the assistance of biosensor associated nanotechnology. This life-threatening disease must be diagnosed as earliest as possible to avoid the disease prolongation correlating with the direct mortality. Integration of nanodevices attempt to solve the issue by acting as boosting agent in mental healthcare system. Initially, nanomaterial blooms widely in biosensing applications in terms of good surface modifier, stability, biocompatible, increase the electrons momentum between the biomarkers and sensing surface and also able to provide a high surface-to-volume ratio. Therefore, utilization of biosensor incorporated nanomaterial for TTC syndrome diagnosis was highly demanded in healthcare department. Various types of nanomaterial play a crucial in determining the stress biomarkers owing to their outstanding key features. Yet, in depth study regarding TTC syndrome diagnosing using biosensor platform still underway but more studies were carried out and able to obtained satisfactory outcomes. Biosensor is capable of operating in mental healthcare system since several studies were done using real clinical samples as discussed. Despite, digital monitoring also was practiced recently in detecting stress biomarkers and updated technology never fails to give good outcomes. Digital monitorization highly contributes to medical department in the way of cost reductions and time consumption for TTC syndrome diagnosing. This review surely a roadway for the researchers in similar field to develop new ideas on fabrication system, electrodes modification using novel nanomaterial, sensitivity of stress biomarker detection and in designing of robust and quick nanodevice for real time applications.

Conflict of Interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1: Four different shapes of left ventricular malfunction were clearly illustrated. This shape determines the acute level of the stress cardiomyopathy. The most dangerous level is dyskinesia of the left ventricular apex and hyperkinesia of basal parts.

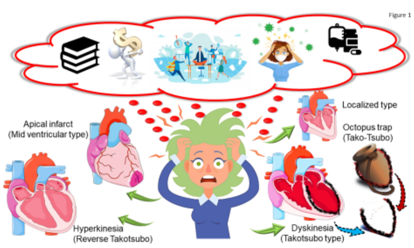

Figure 2: Stress associated human body system. The endocrine system release stress biomarkers (hormone) via three pathways; a) target on the same cell; b) autocrine signaling secretory cell; c) paracrine signaling.

The nervous system plush out the stress biomarkers (neurotransmitter) from nerve cell towards specific muscle, neuron or gland cell. The process is finely illustrated.

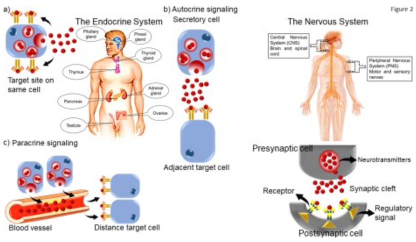

Figure 3: The timeline briefly explains the emergence of biosensor. From conventional to upgraded technologies (nanosensor) are shown. High performance liquid chromatography, capillary electrophoresis, chemiluminescence are the examples of laboratory-based experiments to diagnosis stress cardiomyopathy whereby lab on chip is sensor-based research on fingertips.

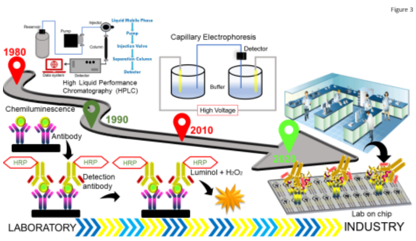

Figure 4: Advantageous of integrating nanoplatform in sensing field. Listed to study the comparison between with and without nanoplatform. Nanoplatform highly contributes to biosensor application in terms of detection outcomes.

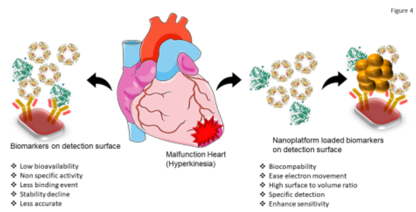

Figure 5: Briefly displays the digital diagnostics for current situation. Stress can be detected by wearing stress detector (mHealth) and can be termed

as ‘Home detection’. The overview of detection process using digital technology was precisely demonstrated.