

Future Strategies for Managing Congestion in Heart Failure Patients Using Cardiac Biomarker-Guided Self-Testing

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Short Communication

Chronic heart failure (HF) is a leading cause of morbidity and mortality worldwide [1], with 5.8 million afflicted in the United States [2], and the American Heart Association predicts that over 8 million Americans will have heart failure by 2030. Nearly 1 million hospitalizations occur annually in the United States for patients previously diagnosed with HF, resulting in an estimated \$34 billion spent each year on HF patient care in just the United States, with ~70% of the annual cost attributed to acute in-hospital care [2-4]. Of the 1 million patients hospitalized annually for HF, approximately 25% are also readmitted within 30 days after discharge [5], resulting in an additional \$2.7 billion per year of hospitalization costs [6].

The primary cause for both the initial hospitalization and readmission of patients previously diagnosed with HF is acute decompensation caused by clinical congestion, as opposed to diminished cardiac output [2,7]. The onset of clinical congestion requiring hospitalization can be subtle, with subclinical congestion preceding clinical congestion by days or weeks before acute decompensation occurs, often suddenly [7]. This observation suggests that improved early management of subclinical congestion before it becomes acute has the potential to reduce both the initial hospitalization as well as rehospitalization rates for many of these HF patients [7,8].

The current standard of care for management of congestion in HF patients includes at-home, serial self-monitoring of weight, careful regulation of oral water volume intake, prescribed medications that improve long-term outcomes in HF, combined with in-person office visits. Unfortunately, this often results in the delay of therapeutic care adjustments until after patients become symptomatic. Once symptomatic, HF patients are more likely to be admitted and/or readmitted for clinical congestion [2]. There is a rapidly growing recognition of the potential for circulating cardiac biomarkers to aid in the pre-symptomatic assessment and proactive management of congestion in HF patients [9,10]. Independent of the initial cause of congestive HF, impairment of the myocardium results in a series of biomarker-associated compensatory mechanisms that can reflect the congestive state [1,10]. The most established of these clinically proven cardiac biomarkers are B-type natriuretic peptide (BNP) and the closely related N-terminal fragment of its prohormone, NT-proBNP, which are released by stretching of the ventricular wall, inducing vasodilation and inhibiting the renin-angiotensin system [10] (Figure 1).

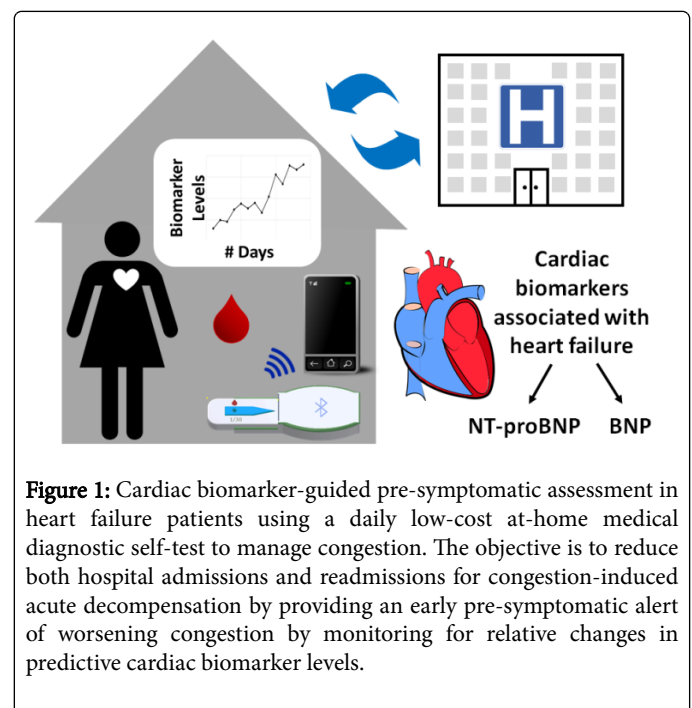


Figure 1: Cardiac biomarker-guided pre-symptomatic assessment in heart failure patients using a daily low-cost at-home medical diagnostic self-test to manage congestion. The objective is to reduce both hospital admissions and readmissions for congestion-induced acute decompensation by providing an early pre-symptomatic alert of worsening congestion by monitoring for relative changes in predictive cardiac biomarker levels.

There have been multiple clinical trials demonstrating the diagnostic utility of monitoring BNP in HF patients [1]. In the "Breathing Not Properly" study, BNP levels targeted at a 100 pg/ml threshold had a sensitivity of 90% and specificity of 73% for diagnosing HF in patients presenting to the ER with acute dyspnea, with the measured BNP level shown to be the single most accurate predictor to identify and differentiate congestive heart failure from other causes of acute dyspnea [11]. In other hospital-focused work, BNP levels >300 pg/mL prior to patient discharge were prognostic of adverse events [12,13], and were also shown to be prognostic when used in outpatient settings [14]. In an outpatient monitoring study, both routine and repeated measurements of BNP using a target threshold of ~125 pg/mL were also shown to lower HF patient risk for readmission [15]. However, one suggested weakness of these studies is that the natriuretic peptide (NP) cardiac biomarker levels may have been measured too infrequently [10]. Additionally, the angiotensin II-receptor neprilysin inhibitor sacubitril-valsartan (Entresto[®]), which is now becoming commonly prescribed for heart failure [16], leads to prolonged levels of BNP in the patient's bloodstream, while NT-proBNP is unaffected by sacubitril-valsartan [17]. This suggests that

NT-proBNP biomarker levels will be more commonly monitored in future work, instead of BNP.

Because of the potential clinical utility of more frequent outpatient BNP or NT-proBNP monitoring to aid in the decision-making for proactive patient care adjustments, recent approaches have been evaluated for serial at-home testing. The HABIT trial was a recent pilot study of 163 patients with HF that evaluated daily fingerstick blood measurements of BNP levels in patient homes for the first 60 days after discharge [18]. This study suggested that daily tracking of relative BNP biomarker levels and trends was a better indicator of HF patient prognosis than strictly relying on a single absolute BNP level at discharge, as well as potentially providing a useful method to monitor for early decompensation. However, there are currently no FDA-approved at-home diagnostic self-tests for NP cardiac biomarkers in the United States. Instead, HF patients need to travel to a clinic or diagnostic lab for serial NP biomarker testing.

At this time, intensive monitoring of cardiac biomarkers has not yet been demonstrated to impact clinical outcomes, but appears to warrant further evaluation. With the right diagnostic technology, it may be possible for HF patients to routinely measure and track circulating BNP or NT-proBNP biomarker blood levels using a fingerstick blood test, similar in practice to the self-monitoring blood glucose tests used today by diabetics. This type of portable, self-test has the potential to be both easy-to-use and relatively inexpensive to aid chronic HF patients in managing congestion. However, both the molecular diagnostic technology and electronics technology used to measure blood glucose levels in existing low-cost, at-home blood glucose self-test kits has a sensitivity in the $\mu\text{g/mL}$ range [19], which is about six orders of magnitude less sensitive than the pg/mL sensitivity required to routinely track pre-symptomatic relative BNP or NT-proBNP cardiac biomarker levels in HF patients [1,18,20].

Colorimetric-based immunoassay technology, commonly used today on the lateral-flow test-strips in pregnancy self-test kits, including newer smartphone-connected digital versions, can improve circulating biomarker detection sensitivity down into the ng/mL range. While the key benefits of colorimetric test strip technology for at-home use is a very low manufacturing cost combined with ease-of-use, a maximum sensitivity in the low ng/mL range [21] severely limits the usefulness of colorimetric immunoassays in providing pre-symptomatic assessments [22-24]. Alternatively, fluorescence-based immunoassays can significantly improve both sensitivity and quantitative analysis compared to existing colorimetry-based immunoassay technology [24,25]. In fluorescence-based immunoassays, a biorecognition capture site on a test strip is actively interrogated with a bright light source, and the emitted fluorescent signal is detected electronically using sensitive readout electronics. Fluorescent biorecognition immunoassay technology offers two to three orders of magnitude higher analytic sensitivity compared to colorimetry and is predicted to provide the required pg/mL sensitivity [21,23,26]. However, conventional fluorescent biorecognition-based diagnostic instruments are relatively complex and expensive desktop-sized machines that typically require routine maintenance, calibration, and cleaning. This renders them problematic for home use, because they require each user (patient) to set up the equivalent of a personal diagnostic lab in their home [23].

One potential at-home solution is a configuration that combines the high sensitivity and quantitative analysis of fluorescent biorecognition-based desktop instruments with the well-recognized convenience, ease-of-use, and low cost of colorimetric lateral flow immunoassay test

strips. In this approach, the colorimetric label is simply substituted with a fluorescent label in the conjugate pad on the test strip, combined with creating a low-cost, easy-to-use instrument to electronically detect the emitted fluorescent signal. To date, the recognized limitation in constructing high-sensitivity fluorescent biorecognition instruments is the need for large and expensive optical components, such as optical microscopes (for magnifying optics), together with lasers, filters, and low-light digital cameras. These optical components then need to be combined with complex and expensive readout electronics [23,27] to electronically detect the emitted fluorescent signals [21,27,28].

As a potential solution to this key limitation, we have developed a low-cost prototype configuration for detecting low-level pre-symptomatic cancer biomarkers that eliminates the need for separate magnifying optics by sandwiching the fluorescent biorecognition layer directly between an inexpensive light source and a silicon photodiode detector [23,29]. This is not a new optical configuration; however, in our approach, we resolved the previously reported poor diagnostic sensitivity by combining very low-cost, high-Q optical emission/excitation filters with low-cost neuromorphic-inspired charge integration electronics. We demonstrated that this new approach can provide high-sensitivity, quantitative fluorescent signal detection into the required pg/mL range using a compact configuration predicted to be similar in cost to the home blood glucose meters used today [23,29].

A key new insight was recognizing that today's rapidly advancing Internet-of-Things (IoT) technology can be combined with computationally powerful smartphone technology to approximate diagnostic laboratory instrument functionality and sensitivity when coupled with fluorescent biorecognition-based lateral flow test strips [29]. IoT electronics technology typically encompasses the large assortment of sensor-enabled smart devices that connect and automatically transfer data via the internet. The thing in IoT, can include: automotive sensors, smart TVs, household electric meters, wearable devices, and even washing machines. All of which are designed to expand our electronic connectivity with the physical world. In this particular case, the thing, is a smartphone-connected biosensor used to test new and emerging circulating biomarkers, combined with the ability to wirelessly report biomarker levels and trends to care providers. For perspective, the analyst firm Gartner conservatively predicts that by 2020, over 20 billion IoT devices will be connected worldwide.

Finally, in an increasingly aging population, redistributing limited healthcare resources to enable more frequent home monitoring of chronic patients may ultimately provide better outcomes for dollars spent. This has the potential to transform healthcare from today's reactive and hospital-centered approach into one much more focused on proactive and person-centered care, thanks to recent advances in molecular diagnostic technology, combined with rapidly advancing low-cost and highly-sophisticated consumer electronics technologies [30].

Competing Interests

Drs. Anderson, Blain Christen and Smith are founders of FlexBioTech, Inc.

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