Original Article

SEPRDD-CHF: A JVP Guided Diuretic Releasing System for Patients with Acute Precipitation over Chronic Congestive Heart Failure

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DOI:10.37821/ruhsjhs.5.1.2020.6-11

ABSTRACT

Introduction: Acute precipitation of congestive heart failure (CHF) is a life threatening condition requiring urgent management, including early detection and treatment with intravenous loop diuretics. An automatic and instantaneous release of loop diuretic (hours before the patient could even seek emergency medical care) will be very useful in aborting/ delaying an impending acute CHF over the preexisting compensated CHF or cor-pulmonale. The present study aimed to design a drug delivery system (SEPRDD-CHF) which is programmed to trigger an instantaneous and automatic release of a diuretic within seconds of rise in JVP above a predetermined cut-off point.

Methodology: In the present study, a functional model of SEPRDD-CHF was first designed. SEPRDD-CHF stands for **SE**nsing JVP **P**ressure and **R**elease of **D**iuretics **D**evice in **CHF** patients. Thereafter, an in-vitro study was conducted to validate the model's functionality in terms of accuracy, sensitivity, and repeatability.

Results: The results showed that the system was functioning as desired and was accurately triggering the release of the desired volume of drug each time the pressure crossed the cut-off point.

Conclusion: Having met the standards of accuracy, sensitivity, and repeatability, the system can now be recommended for pre-clinical testing in animals.

Keywords: Acute precipitation, congestive heart failure, drug delivery system, jugular venous pressure, SEPRDD-CHF.

INTRODUCTION

Congestive heart failure (CHF) is one of the most common chronic conditions in the United States (US) and worldwide, affecting an estimated 5.7 million US population.[1] By 2030, its prevalence is expected to increase by 46%, affecting more than 8 million US adults. Acute precipitation over chronic CHF is a life threatening condition that needs an urgent medical management with loop diuretics. Currently, in the management of acute and chronic CHF, diuretics remain one of the most commonly prescribed drugs in the US and have proven to be an integral component. The use and efficacy of diuretics in improving symptoms of CHF, like dyspnea and edema have also been extensively studied in the past.

In patients with CHF, an elevated jugular venous pressure (JVP) and a third heart sound are each independently associated with adverse outcomes, including progression of heart failure.[1] Elevated jugular venous pressure is a manifestation of abnormal right heart dynamics, most commonly reflecting an elevated pulmonary capillary wedge pressure due to left sided heart failure.[2] This usually indicates fluid overload, necessitating an urgent diuresis that can be achieved by a class of drugs called diuretics. Diuretics have been well established as the first-line therapy for heart failure patients with congestion.[3] A meta-analysis assessing the benefits of diuretics in chronic heart failure showed a decrease in mortality (3 trials, 202 subjects) and worsening of heart failure (2 trials, 169 subjects) in subjects compared to placebo (treatment with

no therapeutic effect).[3] A few clinical trials (4 trials, 169 subjects) have also demonstrated that diuretics improved exercise tolerance in subjects with chronic heart failure compared to active controls.[3] Furthermore, an early detection of acute precipitation over chronic CHF and its early management with intravenous loop diuretics has been found to be associated with lower mortality (Figure 1).[4]

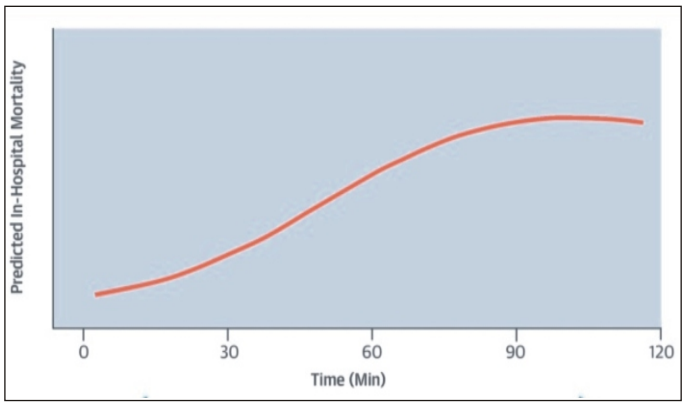

Figure 1: Door-to-diuretics time and in-hospital mortality.[4] (Door-to-diuretics time consists of the time needed to perform evaluation, make a diagnosis, and start intravenous diuretic therapy after patients with acute heart failure arrive at the emergency department).

Such findings suggest that use of a control mechanism (like a drug delivery system) that can continuously monitor jugular venous pressure in patients of CHF may be prudent for an effective and prompt management of an emergent acute precipitation. One such control mechanism can be a JVP-responsive implantable drug delivery system for effecting therapeutic dosing of diuretics.

Various implantable medical devices like pacemakers, joint replacements, etc. are being routinely used in many medical specialties like cardiology, orthopedics, and neurology. The U.S. Food and Drug Administration (FDA) has defined products that combine devices, drugs, or biological products as "combination products"; examples of which include drug releasing transdermal patches, bone grafts, and absorbable sponges or meshes impregnated with antibiotics. A novel class of combination product featuring on-demand drug release capabilities was first described by Santini et al who developed a microchip with many reservoirs containing discrete doses of drug.[5-7] This microchip-based implant, also called as micro-electrochemical system or MEMS-based drug delivery system, is activated by a wireless signal which triggers the micro-reservoirs to release the drug on a pre-programmed dosing schedule. The other drug delivery systems which have been developed in the last few years are micropumps and osmotic pumps among others.

However, in certain cardiovascular diseases like CHF, just maintaining a constant blood level of a drug is not solely desirable; rather, an immediate drug delivery in higher concentrations during the time of greatest need (e.g. acute precipitation) also holds an equal importance. There still remains an unmet dire need to develop a drug delivery system that assimilates the advantageous features of the existing chip based delivery systems with additional desirable features like biocompatibility and ability to release drug when actually required. One seemingly promising alternative can be an implantable drug delivery system designed to release drug in response to some specific physiological or metabolic changes in an individual. This controlled and responsive drug delivery system can prove to be a proficient approach since it will release a therapeutic agent (like Furosemide) whenever the vital parameter (such as the jugular venous pressure) gets elevated. The most valuable advantage of such kind of system will be that it can work in the absence of any hospital facility or even a healthcare provider for an immediate assessment of an impending acute precipitation over chronic heart failure by measuring the JVP and subsequently releasing a diuretic drug such as Furosemide which otherwise is also the first line of treatment of CHF in emergency situations in hospitals.

The primary objective of the present study was to design and validate a functional model of a drug delivery system (SEPRDD-CHF) that is capable of monitoring and controlling a raised jugular venous pressure by releasing stored furosemide as a response for aborting acute precipitation over chronic congestive heart failure. SEPRDD-CHF stands for **SE**nsing JVP **P**ressure and **R**elease of **D**iuretics **D**evice in **CHF** patients.

Based on our current knowledge and experience, no such type of system is in use or in the development pipeline for the management of CHF till date.

METHODS

This was an in-vitro experimental study conducted in the Clinical Pharmacology Research laboratory in the Department of Pharmacology in a University medical

college, Jaipur, Rajasthan. A functional model of the drug delivery system was first designed and constructed and validation tests were then conducted in the laboratory to ensure its functionality, accuracy, repeatability, safety, and electrical compliance.

Drug delivery system: The drug delivery system called SEPRDD-CHF, consists of two main components, namely a thread like sensor which hangs inside the internal jugular vein (IJV) and a reservoir of drug (diuretics). This system can be implanted over the IJV by a very simple technique. As the JVP increases above a predetermined cut-off value, which will be set according to the patient's profile, the sensor gets activated and sends signal to the reservoir drug chip triggering the release of a fixed dose of stored diuretic into the IJV lumen. Also, the system will activate the alarm of a smart phone/ any other electronic device, thus warning the patient to seek medical advice urgently (Figure 2).

In the present invention, as illustrated in figure 3, the system includes a biosensor (1) for sensing the venous pressure and components interconnected together, a bridge rectifier (2) for providing power to the operational amplifier (OP-AMP) circuit, a voltage regulator (3) for regulating the supply to the Transistor-Transistor Logic Circuit, a relay driver (4) for driving relay to operate pump, a microcontroller or a processor (5) for operating the circuit and controlling the feedback for sensor and relay, a plurality of probes (6) for sensor unit, an op-amp (7) for manipulating of the sensor analog output in digital form, a relay (8) for operating pump, a pump (9) for releasing the drug to specific site; and a portable electronic device (10) by alarming synchronous display of results as obtained by the system. The material used to construct various parts of the system, including the casing, microelectronics, and the sensor, were all made with biocompatible materials.

Device validation: The functional model of the drug delivery system was connected to a glass tube partially filled with water and having a marking corresponding to a cut-off pressure value of 8 cm of H_2O. The drug reservoir was filled with 15 ml of drug at the start of experiment. The system software was such programmed that the release of drug (1 ml) was triggered the moment water level in the tube was raised above the cut-off pressure mark (8 cm of H_2O). The system was validated for its accuracy on the basis of the following observations:

a. Whether the release of drug occurred exactly when the marked cut-off pressure (8 cm of H_2O) was crossed.

b. Whether the exact pre-determined volume of drug (1 ml) was released at each trigger.

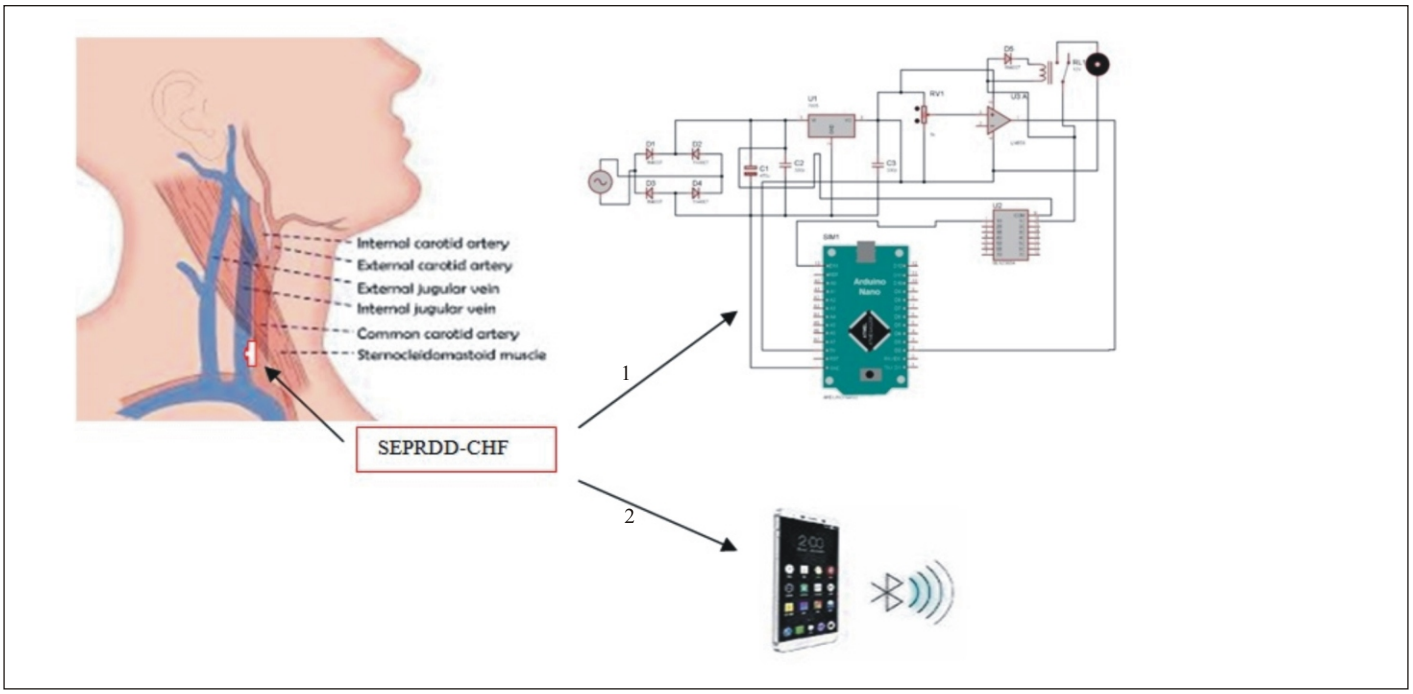

Figure 2: Reservoir drug chip implanted over IJV with a biocompatible thread like sensor hanging inside the IJV.
1. JVP increases > sensor activates >> sends signals to reservoir chip >> diuretic released into IJV lumen and patient gets relief.
2. Also activates alarm of smart phone >> patient seeks medical advice of physician.

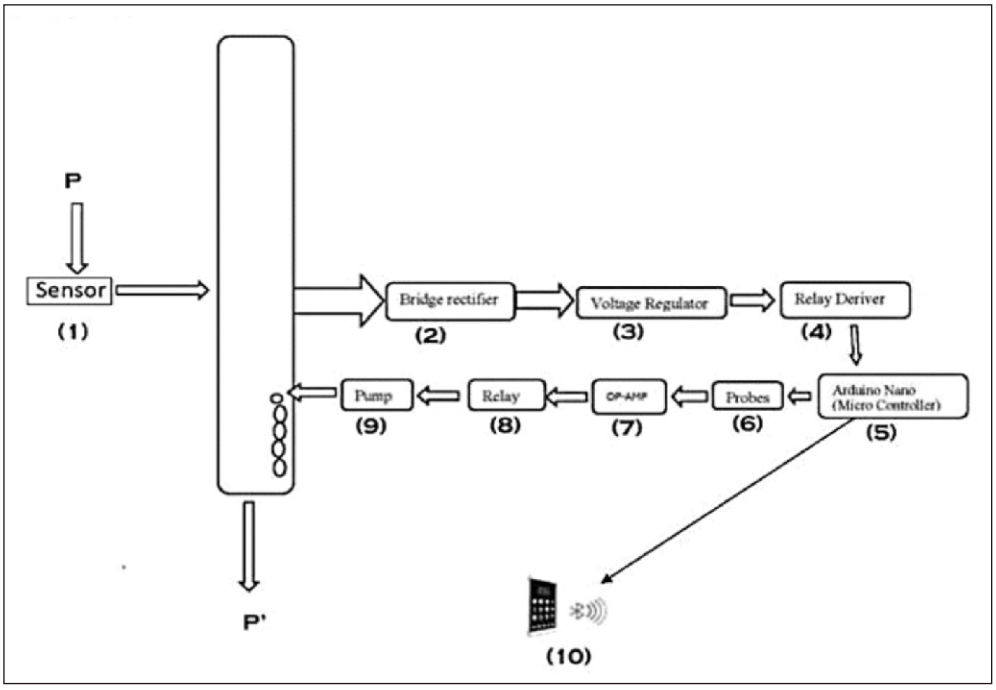

Figure 3: Components of the drug delivery system interconnected together for effecting release of drug at a site on receipt of the biological signal from the sensor.

Table 1: Volume of drug released at each trigger

Series of Experiment	Volume of drug in the reservoir (ml)		Volume of drug released (ml)
	Before trigger	After trigger	
01	15	14	01
02	14	13	01
03	13	12	01
04	12	11	01
05	11	10	01
06	10	09	01

The experiment was repeated several times and both the above mentioned observations were recorded after each experiment in order to validate the functionality of the system in terms of repeatability.

RESULTS

A series of laboratory experiment was conducted and observations were recorded. The accuracy was confirmed since the system consistently triggered the release of drug the moment fluid pressure crossed the marked cut-off pressure value (Figure 4). This observation was seen at all the times (i.e. 100% times) the experiment was repeated. Similar observation was also made related to the volume of drug released. At each trigger, an exactly same volume of drug (1 mg) was released (Table 1).

DISCUSSION

The normal mean JVP, determined as the vertical distance above the midpoint of the right atrium, ranges between 6 to 8 cm H_2O. Deviation from this normal range reflects either hypovolemia (i.e. mean JVP less than 5 cm H_2O) or impaired cardiac filling (i.e. mean JVP greater than 9 cmH_2O). In patients with CHF, elevated JVP and a third heart sound are each independently associated with adverse outcomes, including acute precipitation of heart failure.[1] An early detection of acute precipitation over chronic CHF and its prompt management with intravenous loop diuretics has been found to be associated with lower mortality.

The present invention relates to a drug delivery system

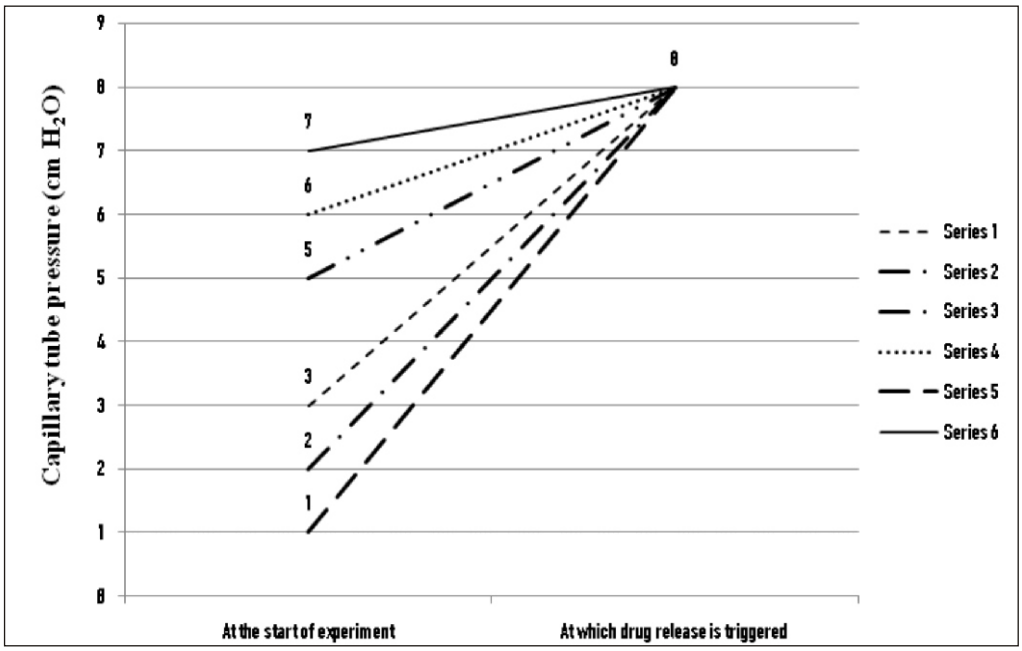

Figure 4: Capillary tube pressure at the time of drug release.

(SEPRDD-CHF) that is programmed to monitor and control JVP in a patient of compensated congestive cardiac failure who is already on optimum medical treatment. This controlled and responsive drug delivery system can be a proficient approach since it will release the therapeutic agent (like Furosemide which is the first line of treatment of congestive cardiac failure in emergency situations) whenever the vital parameter (such as the jugular venous pressure) gets elevated above a cut-off point. The most valuable advantage of this system will be that it can work in the absence of any hospital setting or a healthcare provider for timely assessment and abortion of an impending acute precipitation over chronic heart failure.

The population likely to benefit in particular include diagnosed cases of CHF who are presently on an optimized drug therapy and are in a state of compensated heart failure. The use of this system is, however, suggested only in those patients of compensated CHF who are on medical treatment with a greater tendency to suffer an acute precipitation over CHF due to various reasons like transient arrhythmia, infection, anemia, alcohol intake, or any other cause. Since this device will cause an instantaneous release of furosemide automatically (hours before the patient could even seek emergency medical care), this device will therefore be very useful in aborting/ delaying an impending acute CHF over the preexisting compensated CHF or cor-pulmonale. The device will also, simultaneously, send an alarm signal to the patient's smart phone/ any other electronic device, therefore the patient will also be alerted about the situation. Consequently, the patient may electively plan a visit to her/his treating physician as per her/his convenience and can undergo an evaluation of the acute decompensation with further optimization of her/his treatment.

This will especially benefit those living in remote areas with difficult and delayed accessibility to the emergency medical care due to various reasons (transportation problems, unavailability of doctors, affordability issues, etc).

The present study was an in-vitro study, conducted to validate the functioning of the functional model of a novel drug delivery system. Though seemingly simple, but this was a very important step in the development process of the proposed drug delivery system. Since we have designed an altogether new system of drug delivery, which is presently not being used anywhere in the world, therefore the safety and accuracy of the system was to be ensured first before this system can be tested in either animals or humans in the pre-clinical and clinical phase of device development, respectively. The present study results have shown that the system is functioning as desired and is accurately triggering the release of drug each time the pressure crosses

the cut-off value. Since the concept behind designing this system solely depends upon the accuracy of the system to correctly sense the rise in pressure and also to promptly release the right volume of drug in response, therefore even a small deviation from the set parameters would not have been acceptable. Having met the standards of accuracy, sensitivity, and repeatability, the system can now be recommended for pre-clinical testing in animals.

CONCLUSION

SEPRDD-CHF is a novel drug delivery system that offers a dual benefit of providing prompt treatment and helping the patient to timely seek a consultation by the physician. This may help in reducing the risk of consequent morbidity and mortality by preventing an overt heart failure. This system is in its stage of inception and further exhaustive animal studies are recommended to validate the findings.

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