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ANALYSIS OF USE OF COLLOID NANOPARTICLES FOR MYOCARDIAL DELIVERY IN ULTRASOUND-TARGETED MICRO BUBBLE DESTRUCTION

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Abstract:
Introduction: *Ultra sound (US) targeted micro bubble destruction (UTMD) is a encouraging method for delivering genetic material to the heart. The aim of this study was to test whether colloid nanoparticles can be delivered to the rat myocardium using UTMD and to determine whether tissue damage and contractile dysfunction occurs in hearts exposed to UTMD in vivo conditions.* ***Material and Methods:*** *This descriptive study was conducted in Rural Health Centre Mubarakpur, District Bahawalpur during January 2019 to July 2019. Hearts from anaesthetized rats were exposed to per fluorocarbon-enhanced sonicated dextrose albumin (PESDA) (at two different micro bubble concentrations) and US at peak pressures of 0.6, 1.2, or 1.8 MPa for 1, 3, or 9 min. During US, pairs of 30 and 100 nm fluorescent nano spheres were infused intravenously. Rats exposed to PESDA alone or US alone showed no functional abnormalities, no capillary ruptures, and no nanosphere delivery.* ***Results:*** *The data are expressed with the mean values and mean+1 standard error means (SEM). The differences in nano particulate delivery, premature ventricular contraction (PVCs), and vascular rupture between groups was assessed using a two way analysis of variance (ANOVA), examining the effect of two fixed factors.* ***Conclusion:*** *UTMD allows for colloid nano particles to be delivered to the rat myocardium through micro vessel rupture sites. The efficiency of ultra sound medicines supported local delivery depends on the different things which are applied peak pressure, the time duration of ultra sound exposure, and contrast concentration.*

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INTRODUCTION:

In addition the well-established application of contrast echocardiography for left ventricular opacification and endocardial border augmentation in patients with suboptimal images both at rest condition and during stress are the useful tool for the assessment of myocardial perfusion. There are two possible strategies used for delivering drugs and genes with microbubbles are emerging [1]. The first consists of ultrasound-mediated micro bubble destruction, which is based on the cavitation of microbubbles induced by ultrasound application, and the second is the direct delivery of substances bound to microbubbles which target delivery to sites of endothelial dysfunction in the absence of ultrasound. Different drugs and genes can be incorporated onto the surface of ultrasound contrast agents [2]. It has already been demonstrated that per fluorocarbon filled albumin microbubbles avidly bind proteins and synthetic oligonucleotides. In a similar way, microbubbles can directly take up genetic material, such as plasmids and adenovirus, and phospholipid-coated microbubbles may have a high affinity for chemotherapeutic drugs. The mechanisms by which ultrasound facilitates the delivery of drugs and genes result from a complex interplay among the therapeutic agent the microbubble characteristics, target tissue, the endothelium, and the nature of ultrasound energy [3]. The existence of microbubbles in the insonified field decreases the peak negative pressure required to enhance the drug delivery with ultrasound. This occurs because the microbubbles act as nuclei for cavitation and decreasing the threshold of ultrasound which is energy necessary to cause this phenomenon. Another important therapeutic property of microbubbles is their increased adherence to damaged vascular endothelium [4]. The microbubbles which are coated with albumin do not adhere to normally functioning endothelium, but their adherence to activated endothelial cells or to extra-cellular matrix of the disrupted vascular wall does occur. Because of this characteristic the delivery of genes or drugs bound to albumin-coated microbubbles could be selectively concentrated at the site of vascular injury in the presence or absence of ultrasound application. In 1996, the first published report of targeted DNA delivery was reported using surface ultrasound and intravenously delivered microbubbles carrying antisense oligonucleotides [5].

Objectives of the study

The aim of this study was to test whether colloid nanoparticles can be delivered to the rat myocardium using UTMD and to determine whether tissue damage and contractile dysfunction occurs in hearts exposed to UTMD in vivo conditions

MATERIAL AND METHODS:

This descriptive study was conducted in Rural Health Centre Mubarakpur, District Bahawalpur during January 2019 to July 2019. Male albino rats weighted 300–400g average was selected for this study. They anaesthetized with sodium pentobarbital (60 mg per kg of the body weight). Femoral veins and the left femoral artery of rats were cannulated, to allow fluorescent nanosphere and microbubbles infusion along with the monitoring of arterial pressure.

Experimental Design

Electrodes were attached onto each leg of the rats to allow Echocardiography (ECG) triggered ultra sound emission and it record a six marginal lead ECG. Echocardiography was performed in intermittent mode (1 Hz) with a Sonos 5500 system equipped with a broadband S3 transducer that has a transmit frequency of 1.3 MHz, a bandwidth of about 25% focused at 1.3 MHz, and a greatest peak pressure of this transducer is 1.8 MPa. The transducer was functioned at a depth of 4 cm. Each frame contained 110 lines delivered over a period of 50 ms and forms a 908 sector. Each line was fired as a single eruption of ultra sound with four cycles over 3ms. The tip of the transducer was positioned on the wall of the chest to obtain a view of short axis, at the level of the papillary muscles. This position was sustained throughout the experiments. Mechanical index (MI) was used for the calculation of peak acoustic pressure which is appeared on the system.

Preparation of microbubbles

Per fluorocarbon improved sonicated dextrose albumin (PESDA) which consist of deca-fluorobutane filled albumin microbubble whose mean diameter is 4.2±0.5 mm and a mean concentration is 0.8×10^{9}mL21 was used in this study (Porter et al., 1995). A slow bolus of 200mL of PESDA was suffused intravenously for 30 seconds for every 3 min.

Preparation of Fluorescent Nano spheres

The efficacy of particulate delivery and the relationship between particulate delivery and ventricular function were assessed by continuously infusing a solution containing a mixture of 30 nm green-fluorescent and 100 nm blue or red fluorescent nano spheres into one of the femoral vein catheters. Infusion rate was set at 60uL min^{-1}.

Experimental Analysis

The protocol was designed to assess the consequences of UTMD in the heart in the separate

experiments. There are three phases which are as follows:

1. Instant
2. Sub-acute (24 h)
3. Long-term (7 days)

The effect of ultra sound peak pressure and the time duration of ultra sound exposure on micro vascular integrity and delivery of nano particles were examined in all groups of rats. The heart of rats were randomly exposed to the different peak pressures which are 0.6 MPa for 1 min, 1.2 MPa for 3 min and 1.8 MPa for 9 min.

Two control groups were used for the study of this experiment, which are as:

1. Rats exposed to ultra sound (US) in the absence of PSEDA
2. Rats exposed to PSEDA in the absence of ultra sound (US)

Statistical analysis

The data are expressed with the mean values and mean+1 standard error means (SEM). The differences in nano particulate delivery, premature ventricular contraction (PVCs), and vascular rupture between groups was assessed using a two way analysis of variance (ANOVA), examining the effect of two fixed factors.

RESULTS:

Effects of the duration of US exposure on delivery of nano particles

According to Figure 3 the effect of the duration of US exposure on nano sphere delivery to the anterior wall of the three hearts exposed to a peak pressure of 1.8 MPa for 1.0min, 3.0min , and 9.0 min, respectively. The extent of nano particles delivery gradually increased with the duration of US exposure (to 0.37+0.09, 1.28+0.33, and 4.8+0.8% in hearts). These results explain on the basis of ANOVA.

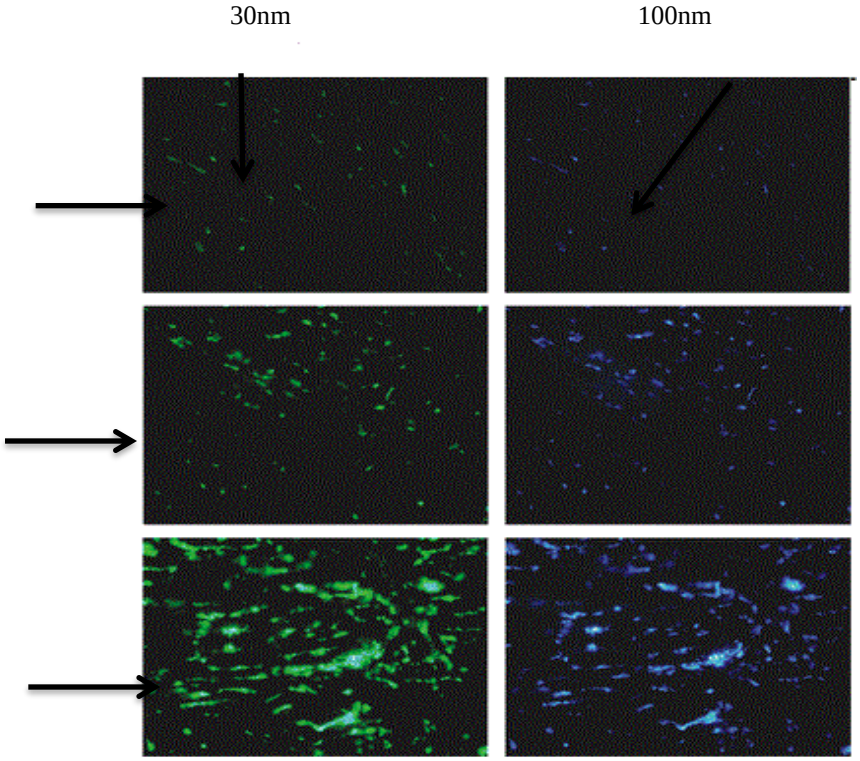

Figure 2: Fluorescent micrographs illustrating the deposition of the 30 nm green- (left) and 100 nm blue- (right) fluorescent nanospheres in hearts exposed to a peak pressure of 1.8 MPa for 1, 3, or 9 min

Effect of micro-bubble concentration on delivery of nano particles

Two groups of rats were selected for this study who received PSEDA in the diluted form or PSEDA un-diluted form. The delivery of nano particles in those hearts was low which received diluted PSEDA as compared to un-diluted PSEDA. In addition, two of the five hearts exposed to diluted PESDA which exhibited no nano sphere particles whereas the remaining three hearts showed mild to diffident nano sphere deposits that were confined to the sub-epicardial layer of the anterior wall.

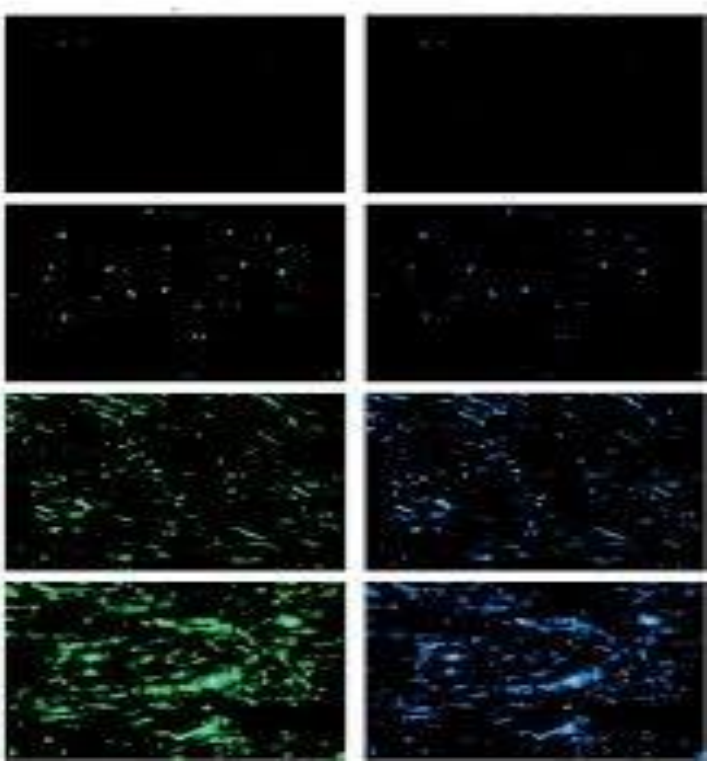

Figure 3: Fluorescent micrographs illustrating the deposition of the 30 nm green- (left) and 100 nm blue (right) fluorescent nanospheres in hearts exposed for 9 min to PESDA alone, in the absence of US or to both PESDA and US at a peak pressure of 0.6, 1.2, or 1.8 MPa.

DISCUSSION:

The main aim of this study was to investigate the role of ultra sound medicines and role of micro bubbles in the delivery of colloid nano particles. Our results specify that effective myocardial delivery of these nano particles can be really achieved using this approach provided that the hearts are being visible for a persistent period of time to both high ultra sound peak pressure and a high concentration of microbubbles [6]. However, the data also indicate that UTMD induces significant bio-effects, which include transient tissue damage and micro vascular ruptures.

Skyba et al were among the first to observe micro vessel ruptures in a solid organ visible in vivo to contrast micro bubbles and ultra sound [7,8]. Afterwards, we made very similar observations in the ex vivo setting of an isolated perfused rat heart preparation.The present study confirms and these previous results by demonstrating that, in vivo as well, the simultaneous exposure of rat hearts to US and contrast microbubbles causes microvessel ruptures and erythrocyte extravasation [9,10].

CONCLUSION:

UTMD allows for colloid nano particles to be delivered to the rat myocardium through micro vessel rupture sites. The efficiency of ultra sound medicines supported local delivery depends on the different things which are applied peak pressure, the time duration of ultra sound exposure, and contrast concentration.

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