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Imaging of Nano- or Micrometer Scaled Soft-Robots within 3-Dimensional Anatomical Structures with Diagnostic Radiological Systems

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Abstract: *In this preclinical study, a wireless and magnetically controllable soft robot, which is designed for use in stroke treatment, is detected under X-ray with different voltage and current parameters in the vessel lumens within the vessel phantoms and ex-vivo tissue materials, using combinations of intravascular contrast agents and bone layer. 60 different images were obtained for each experimental setup by changing the voltage values between 20-90 kilovolts (kV) and current values between 10-170 microamperes (µA). A total of 360 different images were obtained for 6 different setups and evaluated by six different radiologists on a 1-4 point scale according to the visibility of the soft robot in the experimental setup. Visual Grading and Logistic Regression Analysis [1] were used to determine optimal parameters. According to these, when all other variables are held constant, the odds ratio for the kV continuous variable is 1.02605, so a 1 unit increase in this variable is 2.6% more likely to have a better image. When all other variables are held constant, the odds ratio for the µA continuous variable is 1.01811, so a 1 unit increase in this variable is 1.8% more likely to have a better image.*

Keywords: *soft robots, magnetic actuation, pre-clinical models, mechanical thrombectomy, thrombolysis, X-ray imaging, biophysics, radiology.*

1. Introduction

Recently, small-scale robotics become an interdisciplinary field whose popularity has been increasing [2]. Thanks to its very small size and different functions, it is anticipated that such small-sized robots will also be used in the field of health and undertake alternative or complementary functions in treatments. In this study, a wireless and magnetically controllable soft robot was radiologically imaged, which is designed for use in stroke treatment [3]. This research aims at detecting soft robot movements with current imaging techniques and determining optimal imaging parameters.

The main hypothesis in the research is that the aforementioned magnetically controlled mobile microrobot can be imaged by X-ray imaging techniques in phantoms or *ex-vivo* tissues where the physical properties of living tissues are simulated. The fact that no similar study has been carried out on microrobots before in the literature is a limiting factor in terms of comparison. On the other hand, the fact that some of the permanent apparatus functioning in the human body can be seen with X-ray imaging techniques and, in some cases, the apparatus cannot be displayed is related to both the physical environment in which the image is taken and the radiopacity of the apparatus [4].

Our hypothesis is that although it has soft robot features, thanks to the magnetic microparticles it contains, the images of the microrobot can be taken in the optimal parametric value ranges in the most realistic and variable physical environments (the characteristic of the environment, the presence of bone layer and the presence of contrast material in the vascular system). Secondly, evaluating the visibility of the microrobot in the context of parametric variables (voltage and current characteristics of the X-ray device) will be an important reference for future studies as well as confirming the hypothesis.

2. Materials and Methods

2.1. Preparing the Test Environment

The first step of the research includes the preparation of vascular phantoms, in which a soft elastic robot with a stent-like tubular and porous structure will move with magnetic guidance based on anatomical, physiological, and biophysical properties. All phantoms were made using PDMS (Sylgard^{TM} 184, Dow Inc. USA). PDMS was chosen because of its mechanical stability and wide acceptance in biomedical applications [5]. The injection molding technique was used to produce proper lumen geometries [6].

In the next step, a unidirectional circulation system is obtained by combining it with the pulsatile pump (Model 1405 pulsatile blood pump, MA1 55-1838, Harvard Apparatus, USA) assembly. The same setup was also prepared with *ex-vivo* tissue materials.

In the following step, the soft robot has been imaged under X-ray (XPERT 80L, Cabinet X-ray System, KUBTEC Scientific, USA) with different voltage and current parameters in the vessel lumens within the above-mentioned vessel phantoms and *ex-vivo* tissue materials, using combinations of intravascular contrast agents (Iomeron 400, injection solution, Bracco, UK) and bone layer (Cranium model no: 1020162 3B Scientific, Germany).

2.2. Imaging the Robot with X-Ray

The robot was tested under the X-ray imaging technique which is commonly used in minimally invasive endovascular procedures. X-ray imaging visibility of the robot has been demonstrated under various conditions:

1) PDMS phantom is in the vessel lumen,

2) PDMS phantom with contrast agent in the vessel lumen,

3) together with the contrast agent, in the vessel lumen of the PDMS phantom under the simulation model of the cranium,

4) in the arterial lumen obtained from the porcine,

5) in the arterial lumen obtained from the porcine with the contrast agent,

6) in the artery lumen from the porcine under the cranium simulation model, with contrast medium.

Within the scope of X-ray imaging experiments, the robot was imaged both natively in pH:7.4 Phosphate-Buffered Saline (PBS) solution (Gibco, Thermo Fisher Scientific, USA) and with contrast (1:1 ratio PBS and contrast agent -Iomeron 400 solution) with solutions injected into the lumens. Two critical imaging parameters, voltage (kilovolt-kV) and current (microampere-μA), were scanned to find the best imaging results; With the existing imaging systems in the above-mentioned variable environments, the image contents that change as the parameters change have been obtained.

The images are at 10-unit intervals between 20-90 kV in voltage values; current values were obtained between 10-170 μA at intervals of 20 units. However, due to the maximum dose limitation of the device, a maximum current of 160 μA at 50 kV, a maximum of 130 μA at 60 kV, a maximum of 110 μA at 70 kV, a maximum of 100 μA at 80 kV and a maximum of 85 μA at 90 kV. For each test setup, a total of 60 images were obtained. The averages of the scores we prepared for visual grading and given by the radiologist evaluators are saved for each image.

2.3. Visual Grading and Logistic Regression Analysis

As mentioned above, image quality is possible using visual grading and logistic regression analysis methods based on the visibility of structures and their distinguishability from surrounding structures [7,8].

The images were presented to 6 different radiologist evaluators working actively in the field of radiology, who have at least 5 years of professional experience after graduation and have the authority to audit the indications for X-ray and computed tomography according to the radiation protection law applied by the Baden-Württemberg medical chamber (Ärztekammer-BW) in Germany. Evaluators rated their self-assessment on a scale of 1 to 4, using an absolute rating scale due to the lack of previously studied and reference images. Here, 1 point represents the lowest quality images in which the robot cannot be distinguished from the surrounding structures; 2 points for low quality, 3 points for medium quality, and 4 points for expression of high-quality images were used in the evaluation. During the evaluation of the images, a detection monitor in accordance with the European DIN 6868-57 norms was used.

The averages of the scores obtained from the images are plotted in the boxes below the images in the respective tables for each image. In addition, a categorical, ordinal variable in the form of 1, 2, 3, and 4 was created again by taking the average of the given scores and rounding to the nearest integer, and it was evaluated statistically within the scope of ordinal logistic regression analysis method with the help of the polr function in the MASS package in the R program.

The independent variables in the analysis were determined as Volt, Ampere and Setup. In this study, Volt and Ampere variables are continuous, and Setup is a categorical variable with six categories. Since our dependent variable, point, is an ordinal variable, an ordinal logistic regression model was used in this study to examine the effect of independent variables on this dependent variable. The analysis was done with the help of the logit connection function.

3. Results

According to the results we obtained, images were taken by changing the voltage in kilovolts and current in microamperes, which are very important for optimal X-ray imaging, and the optimum parameters were determined in different setups, where the soft-robot was inside the vessel lumen, evaluated by 6 different radiologists within the scope of visual grading.

According to this;

1- For the first setup where only the PDMS phantom is used: 170 μA at 30 kV,

2- For shooting with PDMS phantom + contrast material: 150 μA at 50 kV,

3- With PDMS phantom + contrast material + bone layer: 150 μA at 50 kV,

4- For the soft robot in heart muscle and coronary arteries: 130 μA at 60 kV,

5- For acquisition of heart muscle and coronary arteries + contrast material: 50 μA at 60 kV, 6- With heart muscle and coronary arteries + contrast material + bone layer: 170 µA at 30 kV

values were found to be optimal.

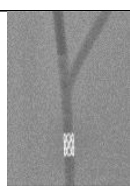
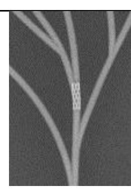
It was concluded that the images obtained at 60 kV and 70 kV, including the values of 69-73 kV, which are generally used for fluoroscopic cerebral angiography imaging [9], can be differentiated from the surrounding structures in all of the images, except the images obtained with 10 µA in setup 3.

According to the visual grading and logistic regression analysis results, since all odds ratio values obtained for the setup variable are less than 1, the values of the images obtained in the Setup 1 reference category are higher than those obtained in all other categories.

- When all other variables are kept constant, we can interpret that the image scores obtained from Setup 2 are 0.31 times better than Setup1.
- When all other variables are kept constant, we can interpret that the image scores obtained from Setup 3 are 0.003 times better than Setup 1.
- When all other variables are kept constant, we can interpret that the image scores obtained from Setup 4 are 0.018 times better than Setup 1.
- When all other variables are kept constant, we can interpret that the image scores obtained from Setup 5 are 0.65 times better than Setup 1.
- When all other variables are kept constant, we can interpret that the image scores obtained from Setup 6 are 0.013 times better than Setup 1.

According to these results, the images obtained from Setup 1 have better visibility than all other sets. The worst viewing was in Setup 3. This relationship is consistent with the scores obtained from the setups. When all other variables are held constant, the odds ratio for the kilovolt continuous variable is 1.02605, so a 1 unit increase in this variable is 2.6% more likely to have a better image. When all other variables are held constant, the odds ratio for the microamperes continuous variable is 1.01811, so a 1 unit increase in this variable is 1.8% more likely to have a better image.

TABLE I: Optimal µA and kV values

Setups	1	2	3	4	5	6
Images						
Optimal values	170 µA at 30 kV	150 µA at 50 kV	150 µA at 50 kV	130 µA at 60 kV	50 µA at 60 kV	170 µA at 30 kV

4. Discussion

In future studies, carrying out the work that is the subject of the study under *in-vivo* conditions can be done. The effects of soft robots' scale will be studied in the future work. In addition, comparative statistical analyses [10] can be performed where the kilovolt and microampere values obtained from this study are not continuously variable, and the obtained numerical values are used categorically.

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