Author's response to reviews

Title: Pullout strength of pedicle screws with cement augmentation in severe osteoporosis: A comparative study between cannulated screws with cement injection and solid screws with cement pre-filling

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Title: Pullout strength of pedicle screws with cement augmentation in severe osteoporosis: A comparative study between cannulated screws with cement injection and solid screws with cement pre-filling

Dear Editor-in-Chief,

Thank you for your letter on August 26 and for the editorial work on the manuscript we submitted to BMC Musculoskeletal Disorders. The authors have read the comments and suggestions made by the reviewers/editors with care. We have rewritten the manuscript and directly incorporated the suggestions to address each of their concerns. All changes in the revised manuscript are highlighted in bold. Our responses to the referees’ comments are listed below, and we deal with each issue in a point-by-point manner. We hope that with these changes our manuscript will meet the criteria for publication in BMC Musculoskeletal Disorders. We thank you again and look forward to hearing from you soon.

Response for reviewer #1:
Thank you for your review.

The authors would like to express our respect for your effort on the review of this manuscript. We have carefully read the comments and suggestions. Below we list your comments and deal with each issue in a point-by-point manner.

Reviewer's comments:
General Comments:
The question posed by the authors is well defined. The methodology is well described by the authors. The data appear to be sound. The manuscript adheres relevant standards for reporting data. The discussions and conclusions are well balanced and supported by the data, however the conclusions are limited in clinical application since the experimental model does not seem representative of osteoporotic bone. The limitations to the study are clearly stated. The authors acknowledge previous work in the area. The title and abstract accurately convey what has been found. The writing in the manuscript is very good.

Major Compulsory Revisions
The only issue I have with the methodology is that the experimental test blocks do not
seem be representative of osteoporotic cancellous bone. Even though the experimental model is described as being extremely osteoporotic, it still seems to be well below the density, porosity, strength and modulus of measured properties of human osteoporotic vertebral bone (1,2).


Reply:
1. The test blocks used was open cell rigid foam developed by Sawbones Worldwide (Pacific Research Laboratories Inc.). The manufacturer’s instruction states: “The appearance of Open Cell Rigid Foam resembles that of human cancellous bone. The cell structure is over 95% open and the cell size is 1.5 to 2.5mm. The Open Cell Rigid Foam does not have as high compressive strength values as the Cellular Rigid Polyurethane Foam, but it is suitable for a variety of applications requiring the open celled structure, such as cement injection and modeling osteoporotic cancellous bone.”


2. In a recent study, Bullmann et al. biomechanically investigated primary and revised cement-augmented pedicle screws in comparison with unaugmented screws using 23 osteoporotic vertebrae from human cadavers. The mean bone density of the osteoporotic vertebrae they used was 52.6 mg/cm$^3$ (That is 0.052g/cm$^3$). In our study, the density of test block we used was 0.088 g/cm3, which is higher than that of Bullmann’s study.


3. Human bone is classified as cancellous if it has an apparent density in the range of 0.09 to 1.26 g/cm$^3$ (Gibson and Ashby, 1988). The compressive and tensile strengths of cancellous bone have been shown to be related to (apparent density), and thus vary by more than two orders of magnitude over a typical range of densities (Carter and Hayes, 1976). In the current study, in order to study the effects of specific parameters related to fixation screws independently from variations in bone material properties and geometry, open cell rigid foam was selected as a test material.


4. Referring to the investigation by Patel et al., they performed the compressive test on different densities (0.32, 0.16 and 0.09 g/cm$^3$) of PU foams to examine whether the commercially PU foams are suitable for mimicking human osteoporotic cancellous bone. They claimed that the fracture stresses of these foams enable them to be used as models for normal (0.32 g/cm$^3$), osteoporotic (0.16 g/cm$^3$) and very low density osteoporotic cancellous bone (0.09 g/cm$^3$). In the current study, considering the ease of cement injection, the PU foam with density of 0.09 g/cm$^3$ was chosen for emphasis of extremely osteoporotic cancellous bone. We believe that although the pullout test did not measure the actual screw/bone interfacial strength, however, the 0.09 g/cm$^3$ PU foam a uniform platform to compare the mechanical behavior of pedicle screws with various designs.

(Patel PSD, Shepherd DET and Hukins DWL: Compressive properties of commercially available polyurethane foams as mechanical models for osteoporotic human cancellous bone. *BMC Musculoskeletal Disorders* 2008, 9:137)

5. The authors are aware that human cadaveric spines will be more clinical relevance instead of test blocks. Unfortunately, we do not have access to human cadaveric spine with severe osteoporosis in our hospital. Although the mechanical/physical properties such as density, porosity, strength and modulus of the test blocks are somewhat different from those of human cadaveric spines, however, the test blocks are the most convenient choice to perform the experiment on circumstance that human cadaveric spines can not be obtained. In our opinion, the choice of synthetic bone is a good one to avoid the influence of biological tissue’s inherent variability. Although the pullout test did not measure the actual screw/bone interfacial strength, the test blocks, however, it provided a uniform platform to compare the mechanical behavior of pedicle screws with various designs.

6. This concern had been incorporated into the limitations/discussion in the revised manuscript. (Page 17, Paragraph 3).
Response for reviewer #2:
Thank you for your review.
The authors would like to express our respect for your effort on the review of this manuscript. We have carefully read the comments and suggestions. Below we list your comments and deal with each issue in a point-by-point manner.

Reviewer's comments:
Major Compulsory Revisions
The authors did carry out a sequence of mechanical tests to evaluate the influence of cement augmentation on spinal screws. The choice of cellular foam is a good one to avoid the influence of biological tissue’s inherent variability. A major topic that this reviewer feels that needs to be addressed is the design of the experiment (DOE). The power of the study is not mentioned and there is no calculation regarding this very important topic. This work is a classic example where the Taguchi DOE or another robust statistical design method can be applied, to precisely find out what factors are the most influential and if interactions exist among them. This should be addressed because the conclusions drawn from the experimental results might change or not have enough credibility due to a low sample size number. Although the reviewer realizes that the experiments have already been carried out, it is advisable to confirm the statistical power and factor/level effects even as a calculation a posteriori. The factors and levels for the experiment need to be explained in an easier to follow fashion. For example, instead of describing the experimental groups in a paragraph, a schematic flowchart would do a better job.

Reply:
1. We thank you for recommending the employ of Taguchi method. Indeed, Taguchi method utilizing an orthogonal array is a useful tool to markedly reduce the total number of required experiments and contains a well-chosen subset of all possible test condition combinations, which can achieve a balanced comparison of levels of any factor.
2. After consulting to a professional statistician, we had employed the Taguchi method to our work. In current study, three factors were considered in evaluating the holding power of a fixation screw inserted into synthetic bone. The three factors were screw shape, cement augmentation technique and screw insertion type, which were further assigned into two levels. Therefore, a total number of 8 trials ($2^3$) were required to identify the relative significance of design factors using a full factorial approach. Below table lists the selected factors and definitions of their corresponding levels.
3. The Taguchi results indicated that, rather than eight trials, only four trials were required to precisely determine the most influential factors. Additionally, after Taguchi's investigation, we also found that the design factor “Cement augmentation technique” was the main influential factor affecting pullout strength, which was consistent with our conclusion that cement augmentation technique for solid screws with retrograde cement pre-filling offer improved initial fixation strength.

4. We appreciate the reviewer’s valuable comment because the Taguchi method can be further employed to analyze studies with more design factors such as screw hole number, screw hole position, screw hole diameter, cement operating temperature…etc, in our future study.

Minor Essential Revisions

Background section

Third paragraph: “Recently, the expandable screw developed for Merck Corporation’s Omega 21 spinal system has increased the interfacial strength…” The Omega 21 was marketed by a company called EBI, which was absorbed by Biomet-Merck, around 10 years ago. The publications mentioned (refs. 6 and 7) are from the turn of the century as well. Please update with newer references. The literature shows very few reports on this particular product.

Reply:
1. The above statement “Recently, the expandable screw developed for Merck Corporation’s Omega 21 spinal system has increased the interfacial strength……” had been replaced with “Another insertion technique is the usage of expandable screw, which allows flange expansion at screw tip and hence increases the screw holding power” in the revised manuscript.

2. The references mentioned in the 1st version had also been replaced with two more recent references (Ref. 14 and Ref. 15)

Fourth Paragraph: “Cylindrical screws are used in most implant systems”
Please cite a reference justifying this statement. Are there actual market share numbers? Why would surgeons prefer one type over another?
Reply:
To our experience, it seems that cylindrical screws are used in most implant systems. To avoid the uncertainty, however, the above statement had been deleted in the revised manuscript.

Methods section
Density of the foam block is 88 kg/m³. A more recent reference by Bullmann et al (see end of this review for a citation) shows actual osteoporotic bone densities in a range almost half of that. Also the ASTM F1839 standard directs that the lowest grade should be (Grade 10, 160 kg/m³ and is higher than your chosen value. Would you care to comment how was this density value chosen?

Reply:
1. We thank you for providing the reference (Bullmann et al.).
2. Indeed, in Bullmann’s study, they biomechanically investigated primary and revised cement-augmented pedicle screws in comparison with unaugmented screws using 23 osteoporotic vertebrae from human cadavers. The mean bone density of the osteoporotic vertebrae they used was 52.6 mg/cm³, which is lower than that of ours. On the contrary, the ASTM F1839 standard defines five grades of rigid polyurethane foam as experimental models for human cancellous bone, and the density of the lowest grade (grade 10) is 160.2 kg/m³, which is higher than that of ours.
3. Cancellous bone is generally reported to have a density in the range of 0.09 to 1.25 g/cm³ [Gibson L, Ashby M: Cancellous bone. In: Cellular Solids: Structure & Properties. New York: Pergamon Press, 1988. 316-331.]. The variations in apparent density, trabeculae orientation, and mechanical properties of cancellous bone within and between specimens are large.
4. Referring to the investigation by Patel et al., they performed the compressive test on different densities (0.32, 0.16 and 0.09 g/cm³) of PU foams to examine whether the commercially PU foams are suitable for mimicking human osteoporotic cancellous bone. They claimed that the fracture stresses of these foams enable them to be used as models for normal (0.32 g/cm³), osteoporotic (0.16 g/cm³) and very low density osteoporotic cancellous bone (0.09 g/cm³). In current study, in order to study the effects of specific parameters related to fixation screws independently from variations in bone material properties and geometry, the PU foam with density of 0.09 g/cm³ was selected as a test material. We believe that although the pullout test did not measure the actual screw/bone interfacial strength, however, the 0.09 g/cm³ PU foam provides a uniform platform to compare the mechanical behavior of pedicle screws with various designs.
Patel PSD, Shepherd DET and Hukins DWL: Compressive properties of commercially available polyurethane foams as mechanical models for osteoporotic human cancellous bone. *BMC Musculoskeletal Disorders* 2008, 9:137

5. The authors are aware that human cadaveric spines will be more clinical relevance instead of test blocks. Unfortunately, we do not have access to human cadaveric spine with severe osteoporosis in our hospital. Although the mechanical/physical properties such as density, porosity, strength and modulus of the test blocks are somewhat different from those of human cadaveric spines, however, the test blocks are the most convenient choice to perform the experiment on circumstance that human cadaveric spines can not be obtained. In our opinion, the choice of synthetic bone is a good one to avoid the influence of biological tissue’s inherent variability. Although the pullout test did not measure the actual screw/bone interfacial strength, the test blocks, however, it provided a uniform platform to compare the mechanical behavior of pedicle screws with various designs.

6. This concern had been incorporated into the limitations/discussion in the revised manuscript. *(Page 17, Paragraph 3)*

Describe the experimental design in detail. Include a statistical power calculation, six samples per experimental group seems a little low number. If needed, seek the help of a biostatistician.

**Reply:**
See reply in previous comment.

How was the insertion rate measured? Even though this is the recommendation from the ASTM standard, the method used in this work should be described.

**Reply:**
The insertion rate for all screws was 3 rev/min was referred to ASTM 543-07. A countdown timer was used to measure the screw insertion rate. *(Page 8, Line 3)*

Continuing with the rate topic, was the flow rate of the cement slurry considered? What was the consistency of the slurry prior to injection? Was there a specific procedure to ensure that the cement had the same conditions in each case?

**Reply:**
The liquid-phase PMMA in a 10-ml syringe was injected into the cannulated screw using a cement injector. The flow rate of the cement was controlled by the injector under a turning rate of half turn in one second until a volume of 3 ml achieved.
Partial screw removal: Why was a 4 minute wait period chosen?

Reply:
All specimens with partial screw removal were 360 degree backed out at four minutes from mixing of cement powder and monomer. This procedure of screw removal has to be done before cement complete curing, and 4 minute was defined based on our surgical experience. With this identical procedure, we believed a reliable comparison of pullout strength can be achieved.

Cement curing time: this is not mentioned in the manuscript. Would the authors consider this to be an influencing factor?

Reply:
PMMA cement used in current was unique (Osteobond bone cement; Zimmer, Warsaw, IN), thus, the cement curing time for all specimens was considered identical. Although cement curing time might be an influencing factor, however, this factor might be excluded due to unique PMMA was used.

Minor typographic/writing errors:
• where it says “Carton” for Instron’s home address, it should be Canton.

Reply:
Thanks for your correction. This error had been corrected in the revised manuscript.

• Please state the complete the name and city of the bone biopsy needle manufacturer, as well as the diameter used (this would influence the flow rate).

Reply:
A statement “A total of 3 ml of cement was then injected into the created hole using a 4-mm diameter bone biopsy needle (Allegiance, Healthcare Co., McGaw Park, Illinois, USA).” had been added in the revised manuscript. (Page 8, Line 18)

Results Section
Typographic error: Second paragraph, last sentence, where it reads: “no significant difference in pullout strength was found between conical and cylindrical screws (p < 0.05)” Shouldn’t the p value be larger than 0.05?

Reply:
Thanks for your correction. This error had been corrected in the revised manuscript. (Page 11, Line 23)
Discussion Section

Change the text in “Their results indicated that the failure force, failure stress and resistance force were highly linearly correlated with the pullout rate”. This sentence would read better like this: “Their results indicated that the failure force, failure stress and resistance force showed a highly linear correlation with pullout strength”. “Pullout rate” should be pullout strength, because the authors only report one value for pullout rate (5 mm/min).

Reply:
1. On this question, we apologize that we don’t understand the reviewer’s intention. In Zdero’s report, they examined the effects of the screw pullout rate on the cancellous bone screw purchase strength at pullout rates of 1 mm/min, 2.5 mm/min, 5 mm/min, 7.5 mm/min, 10 mm/min, 20 mm/min, 30 mm/min, 40 mm/min, 50 mm/min, and 60 mm/min. (Zdero R, Schemitsch EH: The effect of screw pullout rate on screw purchase in synthetic cancellous bone. J Biomech Eng 2009, 131(2):024501)

2. This reference was provided for the purpose to support the usefulness of synthetic bone applied in the in vitro experiment. To avoid the uncertainty, however, this reference had been deleted in the revised manuscript.

The authors mention a composite cement/bone structure in the area of cement infiltration. While this observation is correct, a little more detail should be offered in terms of what type of composite structure they refer to. A simple analysis of a law of mixtures would explain that the difference in density between trabecular bone and bone cement occupying some of the voids (because the porosity will not be completely covered by the bone cement – due to a host of factors such as cement wettability, porosity considerations, flow rate, etc.), is the cause for a much stronger volume of interest leading to the pullout of the bone plus the cement. How would the authors relate this to potential adjacent level damage due to the mismatch of materials’ strength in the operated levels vs. the adjacent (intact) ones? Can the authors offer a way to ensure/measure that the intended amount is actually inside the bone (to account for all of it and avoid leaks)? This is related to the comment the authors make in the last paragraph of the Discussion section: “Third, only one volume (3 ml) of cement was tested. The amount of injected cement may play an important role in determining pullout strength...”. Three comments arise regarding this statement: first, this type of study is precisely what is needed to establish what factor has more influence. Second, the diameter of the screw with respect to the available bone region is important too, maybe more than the amount of injected volume. In cases of slim pedicles, this is crucial. And finally, the failure mode of these screws
may not be necessarily a constant-rate pull-out. What are the comments of the authors to a more physiological-resembling failure method: fatigue testing to create loosening? Please address these comments in your discussion section.

Reply:
1. From observation of the failure specimens after pullout test (Figure 3), PMMA cement infiltration into the open cell of the test block led to a composite cement/bone structure in the area of cement infiltration.
2. For solid screws, cement is prefilled prior to screw insertion. During screw insertion, the prefilled cement is squeezed to occupy some of the voids of the adjacent trabecular bone, which distributes cement on the more proximal threads of the solid screw due to a host of factors such as cement wettability, porosity considerations, flow rate, etc. This causes a difference in density between the bone infiltrated with cement and the adjacent intact trabecular bone. The enormous difference in density between composite structure and intact bone was thought to lead to a general failure mode along the composite/bone interface during axial screw pullout. As the area of the composite/bone interface was greater for the solid screws with retrograde cement pre-filling than for the cannulated screw with cement injection, this increased interface led to significantly higher pullout strength for solid screws.

The above statement had been added in the “Discussion” section. (Page 16, Line 10)

3. The results from experimental work and taguchi analysis indicated that the main factor affecting the pullout strength is the cement augmentation technique, which implies that the more proximal distribution of cement might be the main contributor in improving pullout strength for solid screw case.

Figure captions:
What are the error bars in the graphs? Please state Standard Deviation or Standard Error, where applicable. This should also be addressed in the Methods section.

Reply:
1. The error bars in Figure 4 and Figure 5 represent the Standard Deviation.
2. A Table (Table 2) giving specific values, average and standard deviation for each group was added in the revised manuscript.

Cited Literature:
Many works cited are more than five years old. Please review the latest literature for more up-to-date references and comparisons to your data. There are studies out there very similar to yours, even using the same screws, be sure to cite them. As it is, this
paper would have been cutting-edge in 2000, not 2010. Are there any other expandable screws on the market? Do people use them? Also, please review the latest ASTM standard versions. At least one is already obsolete and has been superseded by a new version.

This paper was mentioned by the reviewer early in these comments:

Reply:
1. Most references provided in the 1st version have been replaced with latest literatures within five years.

2. Reference “ASTM F 543-02” in the 1st version had been replaced with a new version “ASTM F 543-07: Standard Specification and Test Methods for Metallic Medical Bone Screws.” (Ref. 30)
Response for reviewer #3:
Thank you for your review.

The authors would like to express our respect for your effort on the review of this manuscript. We have carefully read the comments and suggestions. Below we list your comments and deal with each issue in a point-by-point manner.

Reviewer's comments:
- Major Compulsory Revisions

“Solid screws were inserted into the test block and then removed to create a hole with identical dimension as the screw contour (conical or cylindrical).” The authors need to clarify this statement. It must be clear to the reader that a screw has already been removed from the PMMA, and thus there is no bond between the tested screw and the PMMA.

Reply:
1. We are afraid that the Reviewer misunderstood the intention of the authors in this statement. Actually, the screw was removed from the prepared pilot hole, not PMMA. The PMMA had not been applied at this stage.
2. To clarify the method for insertion of solid screws, the statement “For solid screws in both conical and cylindrical designs, PMMA cement was pre-filled into the test block prior to inserting the screw. Solid screws were inserted into the test block and then removed to create a hole with identical dimension as the screw contour (conical or cylindrical).” had been revised as “For solid screws in both conical and cylindrical designs, the solid screws were inserted into the test block through the prepared pilot hole and then removed to create a hole with identical dimension as the screw contour (conical or cylindrical).” (Page 8, 2nd paragraph)


“The ultimate pullout force was defined as the maximum load sustained before failure.” The exact definition of failure must be described (i.e. instantaneous loss of 10% of measured load).

Reply:
1. For simple comparison of screw holding power between groups, the peak force in the recorded force-displacement cure was defined as the failure force required to pull screw out of the test block.
2. The statement had been revised as “The peak force recorded during the pullout
test was defined as the maximum pullout strength for comparison”. (Page 9, Line 14)

“The force-displacement curves were then used to determine the failure point of each sample.” Describe failure point. Is it the same as failure displacement or is it the location of failure between screw and block.
Reply:
1. As the previous comment, for simple comparison of screw holding power, the peak force in force-displacement curve was defined as the failure point and was selected for comparison between groups.
2. The mentioned statement had been revised as “The peak force recorded during the pullout test was defined as the maximum pullout strength for comparison.” (Page 9, Line 14)

4. Paragraph reference: Results – Figure 6.
Figure 6 -- A table giving specific values and the corresponding p-values should be added to the manuscript.
Reply:
As per the reviewer’s comment, a Table (Table 2) giving specific values and the corresponding p-values was added in the revised manuscript.

“The radiological photographs (Fig. 5, top) indicated that the area of the cement/screw interface was greater for solid screws with retrograde cement pre-filling than for cannulated screws with cement injection.” Is this a qualitative measure? Data demonstrating the area between cement and screw should be presented. The authors argue that the cement/screw interface is the primary factor for increased pullout strength, however, no quantitative data is presented to demonstrate this hypothesis.
Reply:
1. We apologize for the error that “cement/screw interface” should be corrected as “composite/bone interface” because the observation of the failed specimens indicated that the failure occurred at the composite/bone interface for all cases. This error had been corrected throughout the revised manuscript.
2. The authors are aware that a quantitative measurement of the composite/bone interface will be more convincible to support our statement. Unfortunately, in this study, the area of the composite/bone interface is only a qualitative observation. However, all specimens exhibit an obviously greater area of the composite/bone interface for solid screws with retrograde cement pre-filling.

3. Theoretically, the pullout force required to remove the composite structure (bone with cement infiltration) from adjacent intact trabecular bone is proportional to the composite/bone contact area. Consequently, we believe that a greater area of the composite/bone interface will be beneficial for anchoring strength of the screw.

4. The above statement had been added in the revised manuscript. (Page 16, Line 19)

- Minor Essential Revisions

   Reference(s) Requested: “Almost all of the current research on pedicle screw pullout has been performed with cylindrically shaped pedicle screws.”
   
   Reply:
   1. This statement has been revised as “Our review of literatures found most of the current research on pedicle screw pullout has been performed with cylindrically shaped pedicle screws”. (Page 4, Paragraph 4)
   2. Several references had been added in the revised manuscript. (Ref. 4,5,7,18-20)

   Reference(s) Requested: “Theoretically, conical screws should progressively compress the surrounding bone with each turn of the screw during insertion. This compression of the surrounding bone should be beneficial by providing increased purchase during screw insertion. However, as a result of the rapid reduction in the compression of the surrounding bone if the screw is partially removed to adjust the screw placement during surgery, the reduction of the compression stress could also cause a rapid reduction in the fixation strength.”
   
   Reply:
   Two references supporting this statement were added in the revised manuscript. (Ref. 24 and Ref. 25)

   Please describe the term “retrograde cement”.

14
1. A 4 mm diameter bone biopsy needle was used for cement injection. A mark was made with aseptic marking pen on the needle. The length from the marking point to the needle tip was 5 mm shorter than the length of selected screw. Then the biopsy needle was inserted into the prepared pilot hole until the marking point approached the entry edge of the test block. Cement was then injected into the pilot hole accompanied with a progressively movement of the biopsy needle out of test block until a total volume of 3 ml bone cement was injected. With this technique, a uniform distribution of cement can be achieved.

2. The above statement had been added in the revised manuscript. (Page 8, Paragraph 2)


Group allocation may be better represented in table or figure form. Essentially, you have two groups (conical and cylindrical) which is further divided into sub-groups (retrograde cement, injection, and none) which is further divided into two sub-groups (back-out and not). One figure showing this division would be nice.

Reply:
As per the reviewer’s comment, a Table (Table 1) representing group allocation was added in the revised manuscript.


“For all specimens, a total of 3 ml of cement was injected into the cannulated screw.” What was the pressure or rate at which the cement was injected? Injection rate/pressure would undoubtedly be a factor controlling the infusion of PMMA into the test block.

Reply:
The liquid-phase PMMA in a 10-ml syringe was injected into the cannulated screw using a cement injector. Although the injection pressure was not measured during injection, however, the injection rate was controlled by the injector under a turning rate of half turn in one second until a volume of 3 ml achieved.


Reference(s) Requested: “After the specimens were mounted, pullout force was applied at a constant crosshead rate of 5 mm/min.”

Reply:
ASTM F543-07: Standard Specification and Test Methods for Metallic Medical Bone Screws, defining a crosshead rate of 5 mm/min has been added in the revised manuscript. (Ref. 30)

   “The relationship between force and displacement was recorded in 0.1-mm increments.” This would be better expressed in term of Hertz.

   **Reply:**
   1. As the crosshead rate was 5 mm/min (0.083 mm/sec) and the data was acquired in 0.1 mm increments, the frequency for data acquisition would be \( \frac{0.083 \text{ mm/sec}}{0.1 \text{ mm}} \), which equals to 0.83 Hz.
   2. The above statement had been revised as “The relationship between force and displacement was recorded in 0.1-mm increments (0.83 Hz).” (Page 9, Paragraph 2)

We look forward to hearing from you soon. Thank you very much again.

Sincerely,

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