Journal of Plastic, Reconstructive & Aesthetic Surgery (2016) 69, 1588–1597

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Radiographic evaluation of vessel count and density with quantitative magnetic resonance imaging during external breast expansion in Asian women: A prospective clinical trial

Yujin Myung, Heeyeon Kwon, Changsik Pak, Hobin Lee, Jae Hoon Jeong, Chan Yeong Heo*

Department of Plastic and Reconstructive Surgery, Seoul National University Bundang Hospital, Seoul National University, South Korea

Received 3 March 2016; accepted 14 September 2016

KEYWORDS
Breast reconstruction;
External expansion;
Clinical trial;
Vessel count;
Density;
ASIAN breast

Summary *Background:* Breast augmentation with fat transfer does not bear the risks associated with silicone implantation. The method can potentially be especially useful in Asian women, who often reject augmentation mammoplasty with implants. This prospective clinical trial evaluated the effects of external breast expansion on breast density and vessel count using magnetic resonance imaging.
Methods: Thirty-four enrolled patients were instructed to apply one of two devices, the conventional BRAVA device (used in the AESTES trial) or a novel external expansion device (EVERA) designed for Asian women, continuously for 8 h per day for 12 weeks. For external expansion, the pressure was set to 25 mmHg. Follow-up examinations were performed for 4 weeks after completion of the expansion. The ratio between the fibroglandular and adipose tissues of the breast was measured using T1-weighted MRI, and the number of vessels in the breast tissue was determined before and after the treatment by contrast MRI. Additionally, the volume of the breast was measured by laser scanning before, during, and after the device application. The obtained measurements were compared within and between the groups at different time points.
Results: Six patients dropped out, while 28 completed the trial without major side effects or adverse events. External expansion significantly increased breast vessel count in both the EVERA and AESTES groups ($p = 0.019$, $p = 0.022$). However, it did not significantly change breast density in either group ($p = 0.186$, $p = 0.638$). No significant intergroup differences

* Corresponding author. Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do 463-707, South Korea. Fax: +82 (0)31 787 4055.
E-mail address: lionheo@snu.ac.kr (C.Y. Heo).

http://dx.doi.org/10.1016/j.bjps.2016.09.019

were noted in vessel count ($p = 0.874$) or density ($p = 0.482$). Breast volume increases after 12 weeks of application were statistically significant in both groups, with mean changes of 81 ± 22 cc (AESTES) and 98 ± 30 cc (EVERA) ($p < 0.001$ in both cases).
Conclusions: External expansion resulted in a marked increase in breast vessel count but did not affect breast density. The observed increase in breast volume can be considered substantial for Asian women.
Level of evidence: Level II, therapeutic study.

Background

Many women around the world desire to have aesthetically pleasing breasts. Although the demand for augmentation mammoplasty is high in both Asian and Western populations, breast procedures represent <2% of all surgical procedures performed in Japan and South Korea, compared with >22% in the United States.[1] Although breast augmentation with silicone implants have been proven to be safe and effective, with technical developments in both implant manufacturing techniques and surgical approaches, its popularity is significantly lower in Asian countries.

Breast augmentation with autologous fat transfer has recently gained increased attention owing to technical refinements over the past 10–15 years.[2–5] The use of autologous fat tissue for breast augmentation has many important advantages, as the procedure cannot cause a foreign body reaction and leaves no obvious postoperative scars. Nevertheless, because of the low survival of the transferred fat, the results are largely unpredictable, and mega-volume fat grafting remains controversial in plastic surgery. To increase the survival of the transferred fat, the American External Soft-Tissue Expansion System (AESTES, commercial name BRAVA) was developed in the 1990s by Dr. Khouri and colleagues, and successful results have been published in numerous subsequent reports.[6–9]

There have been many reports on successful mega-volume fat grafting to pre-expanded breast tissue for both cosmetic and reconstructive purposes.[6,7,9] However, as the breasts of Asian women are smaller than those of women of other ethnic backgrounds and have obvious differences in tissue and skin characteristics,[10–12] there has been no clinical trial in an Asian population. Additionally, although researchers have theorized that externally expanded breasts have increased vascularity, no experimental evidence has been obtained or analysis of vascular changes conducted. The present study was a prospective clinical trial in South Korean women undergoing external breast expansion with either the BRAVA device (used in the AESTES study) or a newly developed external expansion device (EVERA) that was better suited to the posture and body proportions of Asian women. The aims were to determine the effects of external breast expansion in Asian women, quantify the results in an objective manner, and identify any changes in breast vessel count by performing a quantitative analysis with enhanced magnetic resonance imaging (MRI) before and after the device application.

Patients and methods

Patients

This study followed the guidelines of the 1975 Declaration of Helsinki, was approved by the Institutional Review Board and Ethics Committee, and was performed under the regulations of the Korean Food & Drug Administration (KFDA). To ensure the reliability of the obtained data, three clinical research associates from the Review Board (IRB) routinely visited our clinic for validation and monitoring. The participants received sufficient explanation of the trial to be well informed before they were enrolled in the study, and written consent to participate was received from all of them.

A total of 34 patients were enrolled in the study after confirmation of the sample size by power analysis. The number of patients was corrected according to the dropout rate of 20% in a previous study. The patient age ranged from 19 to 40 years (mean: 26.6 ± 4.2), and the body mass index was 23.6 ± 3.0 kg/m^2. Individuals with a history of breast surgery and those who were pregnant, active smokers, or had an active infection, diabetes, cancer, or connective tissue diseases were excluded from the study. The patients were randomly divided into two groups (AESTES or EVERA) (Table 1).

Treatment procedure

According to previous studies on external expansion of the breast,[3,6,7,9,13] the duration of external device application varied from 4 to 18 weeks, and the mean daily application time ranged from 8 to 20 h. To minimize dropout rates, which were found to be excessively high in numerous previous studies of external expansion, a shorter daily application time of 8–12 h was recommended to the participants. The total length of the clinical study was 16 weeks, including 12 weeks of device application and 4 weeks of post-expansion follow-up.

After cleansing both breasts, an adequately sized external expansion device was selected, and the pressure control was set to 25 mmHg. To maintain the device in the correct position, a brassiere-shaped jacket was placed over

Table 1 Patient demographics and total application time.

		Age	BMI (kg/m^2)	Breast volume (cc)	Cup size*	Application time
AESTES group	N	17	17	17	17	14
	Mean ± SD	27.6 ± 6.3	23.2 ± 1.8	1083 ± 168	AA (6), A (5), B (3), C (3)	737.1 ± 47.1
EVERA group	N	17	17	17	17	14
	Mean ± SD	30.1 ± 5.7	23.9 ± 3.3	1207 ± 175	AA (7), A (5), B (4), C (1)	739.1 ± 88.8
Total	N	34	34	34	34	28
	Mean ± SD	28.9 ± 6.1	23.5 ± 3.0	1127 ± 170	AA (13), A (10), B (7), C (4)	738.1 ± 69.8

*Cup size: Based on measured breast circumference on nipple height. AA(6 inches), A(7), B(8), C(9).

the device. The patients were instructed to apply the device continuously for a minimum of 8 h at the same time every day.

Study flowchart

The first assessment was performed 6 weeks prior to device application. The patients were evaluated for eligibility to enroll in the study, and written consent was provided. Medical photographs and breast measurements were obtained, and breast MRI (Ingenia 3.0T, Philips) and three-dimensional scanning (Vivid 9i scanner, Konica Minolta) were performed.

After 2, 4, and 8 weeks of device application, patients visited our clinic to undergo a routine examination, measurements of breast size, and three-dimensional scanning. A posttreatment MRI examination was performed at 12 weeks in all patients. Additional follow-up was performed 2 and 4 weeks after completion of device application (Figure 1).

Efficacy assessment

Primary measures

Breast vessel count and density as determined from MRI examinations at the baseline and after 12 weeks of device application were compared. Radiologic findings were assessed by four independent observers, including a board-certified radiologist. Breast density measurements were performed as described by Klifa et al.,[14,15] with some modifications. The original method involves highly complex steps with semiautomatic segmentation by utilizing Bezier splines and Laplacian of Gaussian filter and comparison of each segment after delineation of specific regions. We simplified the method and concentrated on calculating the area of dense tissue by marking the borders of the high-intensity area (dense fibroglandular tissue) and the low-density area (adipose tissue) surrounding the fibroglandular tissue in T1-weighted images. The marking was done by board-certified breast radiologists and trained physicians. Total counts of pixels were calculated with ImageJ software (NIH, Bethesda, MD), and the total volume was calculated as a sum of volumes of separate 2-mm sections from the top to the bottom of the breast. Images were acquired by an Ingenia 3.0T scanner (Philips Healthcare) equipped with bilateral-phased array breast coils. Fat suppression with three-dimensional gradient recalled echo sequence was enabled, with a TR/TE ratio of 4.19/2.30 and a flip angle of 12°. A total of 100 slices were acquired with a thickness of 2 mm, and no gating or weighting protocols were used during the scanning. Precontrast MRI data was used in density measurements. Fibroglandular tissue with high MR density was recognized in accordance with the BIRADS classification. Every sixth axial slice was marked from the upper to the lower level, including the nipple area; the breast outline and boundaries of high-density glandular tissue were delineated, and the ratio was calculated for density quantification. To evaluate breast vessel count, a modified version of the 4-point breast vessel count scale proposed by Martincich et al.[16] was used as a reference for analysis of dynamic contrast MRI images by the abovementioned method. The number of vessels over 20 mm in length and 1.5 mm in maximal transverse diameter was counted in the 3D reconstructed volume using a workstation (Extended Brilliance Workspace, Philips Healthcare) (Figure 2).

Baseline and posttreatment breast volumes obtained by three-dimensional scanning were compared within each group, and treatment results were assessed by comparing the AESTES and EVERA groups. The Vivid 9i scanner is a non-contact three-dimensional digitizer that offers laser scanning and dimensional inspection with the triangulation light-block method, with the accuracy and precision within 0.05 mm. Measurement of breast volume by using three-dimensional scanning has not been validated or published elsewhere, and it is a novel outcome measure in a clinical trial. Digital three-dimensional data were transferred to the Polygon Editing Tool, version 2.0 (Konica Minolta, Tokyo, Japan), and accurate volumes of the breasts beyond the chest cage were obtained for every patient using the CAD data (Figure 3).

Secondary measures

Breast volumes measured 8 weeks after treatment initiation and 4 weeks after completion of device application were compared with baseline data. Results were compared between the groups and time points.

Safety assessment

To assess treatment safety and risk, every adverse event that occurred after obtaining written consent was recorded and analyzed. For risk assessment, the total number of adverse events and the rate of patients that

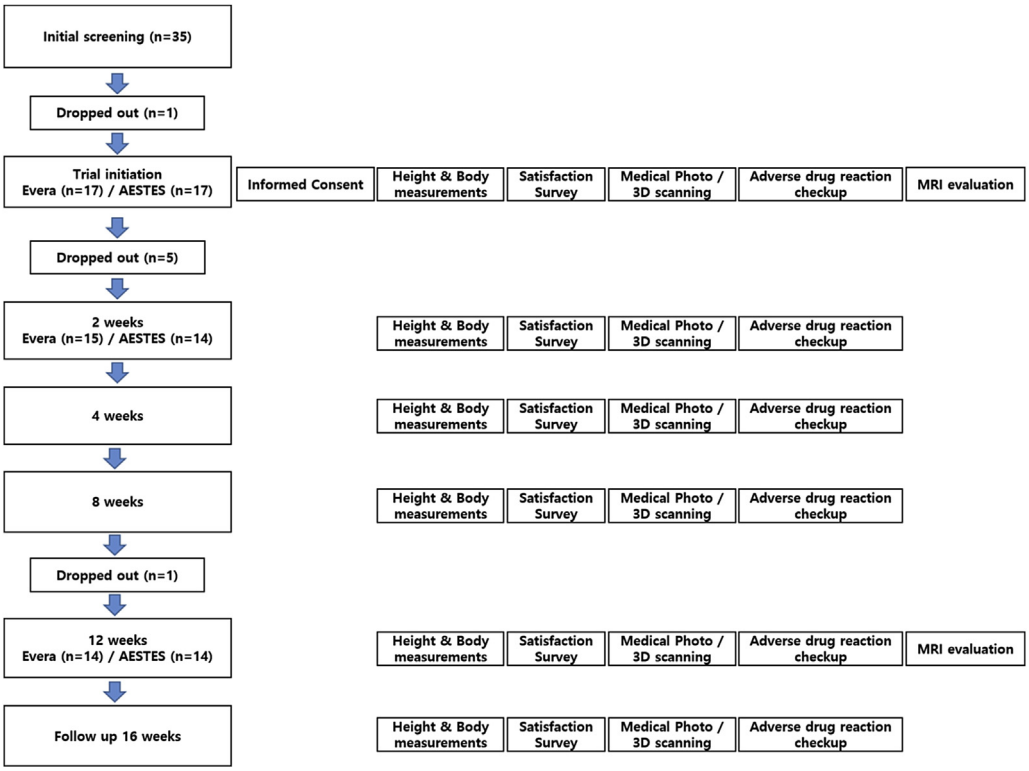

Figure 1 Timetable of the clinical trial.

experienced adverse events more than once were determined. Independent observers who did not participate in the study determined whether a relationship existed between an adverse event and device application.

Statistical analysis

The level of two-tailed statistical significance was set to 0.05 for comparisons of pre- and posttreatment results and intergroup comparisons. Descriptive statistics were used for differences in breast volume changes, and the Mann—Whitney U test was used for intergroup comparisons. Intragroup comparisons for device performance evaluation were made with the Wilcoxon signed-rank test. Testing for normality was performed with Friedman's two-way analysis of variance by ranks for intragroup comparisons of different time intervals. The Mann—Whitney U test was used for intergroup comparisons, and testing for normality was performed with the Shapiro—

Wilk test. In addition, repeated-measures analysis of variance (RM-ANOVA) was used to analyze the repeated breast volume measurements obtained from all participants at the first visit; after 2, 4, 8, and 12 weeks of application; and 2 and 4 weeks after completion of the 12-week treatment.

Results

Six patients dropped out of the trial because of treatment discontinuation ($n = 5$) or failure to attend the examination at the end of the 12-week treatment period ($n = 1$). Among them, three were from the EVERA group and the other three from the AESTES group. The mean age of the patients enrolled in the trial was 30.1 $\pm$ 5.7 years, and the total application time was 739.1 $\pm$ 88.9 h. The pre-application volumes of the right and left breasts were 1029 $\pm$ 194 cc and 1282 $\pm$ 370 cc, respectively.

Primary measures

Vessel counts were obtained and density was assessed by four independent observers (including two board-certified radiologists) before the start of device application and after completion of the 12-week treatment (Figures 4 and 5). An intragroup comparison showed a notable increase in vessel count in the EVERA group, with the pretreatment vessel count of 3.1 $\pm$ 1.1 (95% CI: 0.92—5.31) and the posttreatment count of 3.7 $\pm$ 1.5 (95% CI: 1.04—6.67) ($p = 0.019$) but no statistically significant difference in density (56.0 $\pm$ 11.0% vs. 50.2 $\pm$ 10.6%, $p = 0.186$). In the AESTES group, there was also a notable difference in vessel counts, with the pre- and posttreatment values of 3.1 $\pm$ 1.8 (95% CI: -0.41—6.55) and 3.5 $\pm$ 1.9 (95% CI: 0.24—7.28), respectively ($p = 0.022$). There was no difference in density ratios before and after the treatment (before: 43.6 $\pm$ 8.1%, after: 45.8 $\pm$ 9.3%, $p = 0.638$). The groups did not differ in vessel counts ($p = 0.874$) and density ($p = 0.482$) (Table 2).

The values of bilateral breast volume were significantly different between the baseline and week 12 within both treatment groups (Figures 6 and 7). The average expansion volume in the AESTES group was 81 $\pm$ 22 cc versus 98 $\pm$ 30 cc in the EVERA group. The intergroup comparison

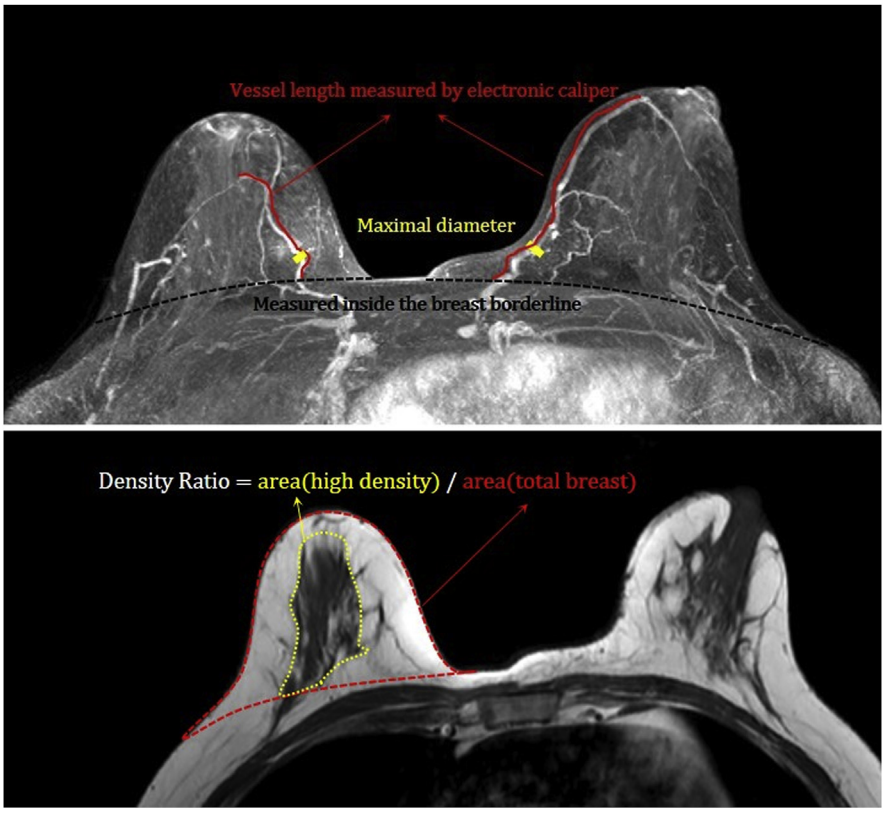

Figure 2 Schematic representation of magnetic resonance imaging analysis of breast vessel count (top) and density (bottom). Breast vessels with a length over 20 mm and a maximal diameter over 1.5 mm were counted, and the numbers before and after the treatment were compared. Density was calculated as the ratio of high density area to total breast volume. Separate sections were analyzed and combined for comparison.

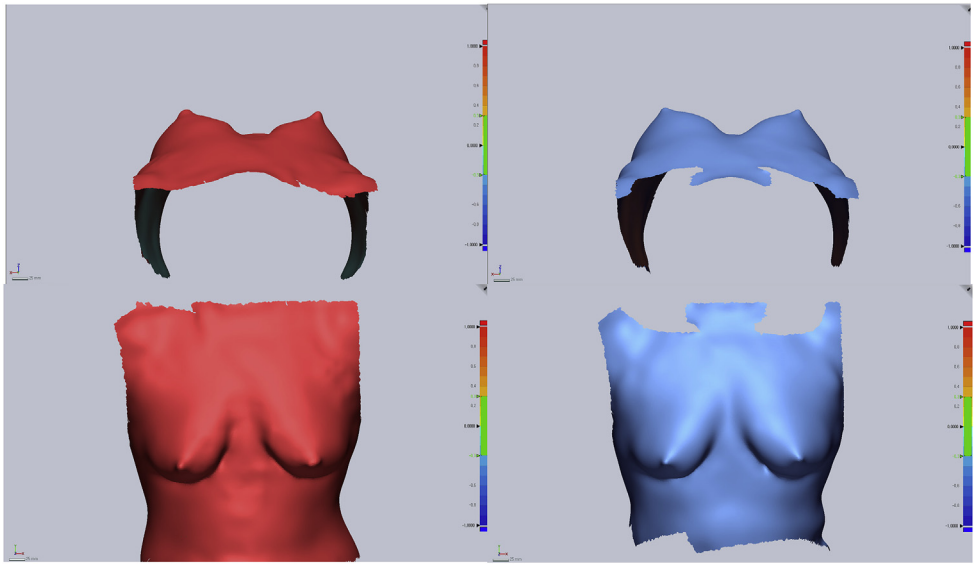

Figure 3 (Left, top and bottom) Three-dimensional scan data obtained at the baseline with the Vivid scanner. (Right, top and bottom) Three-dimensional images after the completion of expansion. Breast volume was measured at each visit, and results were compared retrospectively.

revealed no significant differences in the baseline and 12-week bilateral breast volumes (Table 3).

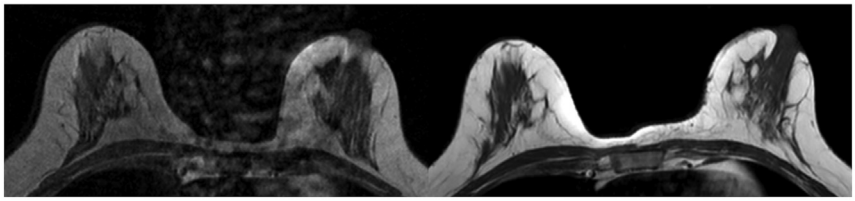

Figure 4 A 28-year-old woman before (left) and after (right) 12 weeks of AESTES use. Posttreatment photographs were obtained 1 month after treatment cessation.

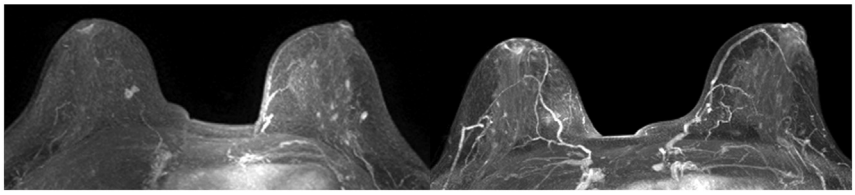

Figure 5 A 38-year-old woman before (left) and after (right) 12 weeks of EVERA use. Posttreatment photographs were obtained 1 month after treatment cessation.

Table 2 Vascularity and density changes. Mann–Whitney U test was used with two-tailed statistical significance set to $p < 0.05$.

Group		Pretreatment (Vessel count)	Posttreatment (Vessel count)		Pretreatment (High density area %)	Posttreatment (High density area %)	
EVERA	n	14	14		14	14	
	Mean	3.1	3.7	$p = 0.019$	56.0	50.2	$p = 0.186$
	SD	1.1	1.5		11.0	10.6	
AESTES	n	14	14		14	14	
	Mean	3.1	3.5	$p = 0.022$	43.6	45.8	$p = 0.638$
	SD	1.8	1.9		8.1	9.3	
Total	n	28	27		28	28	
	Mean	3.1	3.6	$p = 0.015$	48.9	47.7	$p = 0.276$
	SD	1.5	1.7		9.1	10.1	

Secondary measures

After 8 weeks of device application, statistically significant ($p = 0.011$, $p = 0.007$) differences in breast volume compared to the baseline measurements were found for both breasts in the AESTES group. However, in the EVERA group, a statistically significant difference was found for the right breast ($p = 0.030$) but not the left breast ($p = 0.152$). An intergroup comparison revealed no differences.

Left and right breast volumes measured 4 weeks after completion of the 12-week treatment showed significant increase compared to baseline measurements in both groups (AESTES: $p = 0.003$, $p = 0.000$; EVERA: $p = 0.000$, $p = 0.000$ for the left and right breasts, respectively). There were no statistically significant differences between the two treatment groups ($p = 0.579$, $p = 0.336$).

Safety assessment

Adverse events were recorded for all patients who participated in the trial. Five patients in the AESTES group (7/17, 41.4%) and 7 patients in the EVERA group (7/17, 41.4%) experienced adverse device-related events (ADEs). ADEs included application site rash ($n = 13$), application site pruritus ($n = 9$), and application site hives ($n = 1$). The symptoms were not severe for any of the events, and they were relieved during posttreatment follow-up. No other unexpected or serious ADEs were noted.

Discussion

It is well-known that breasts of Asian women have smaller volume and greater density than those of Caucasian or African women. While it appears natural to expect an increased demand for breast augmentation in Asian women, the incidence of breast surgery among all cosmetic surgeries is low, and especially so in women from eastern Asia. Unavoidable incisional scarring from silicone implant insertion and fear of unwanted complications such as capsular contracture, rippling, double bubble, and unnatural postoperative appearance, are the main causes of the lower incidence of breast augmentation in Asia.

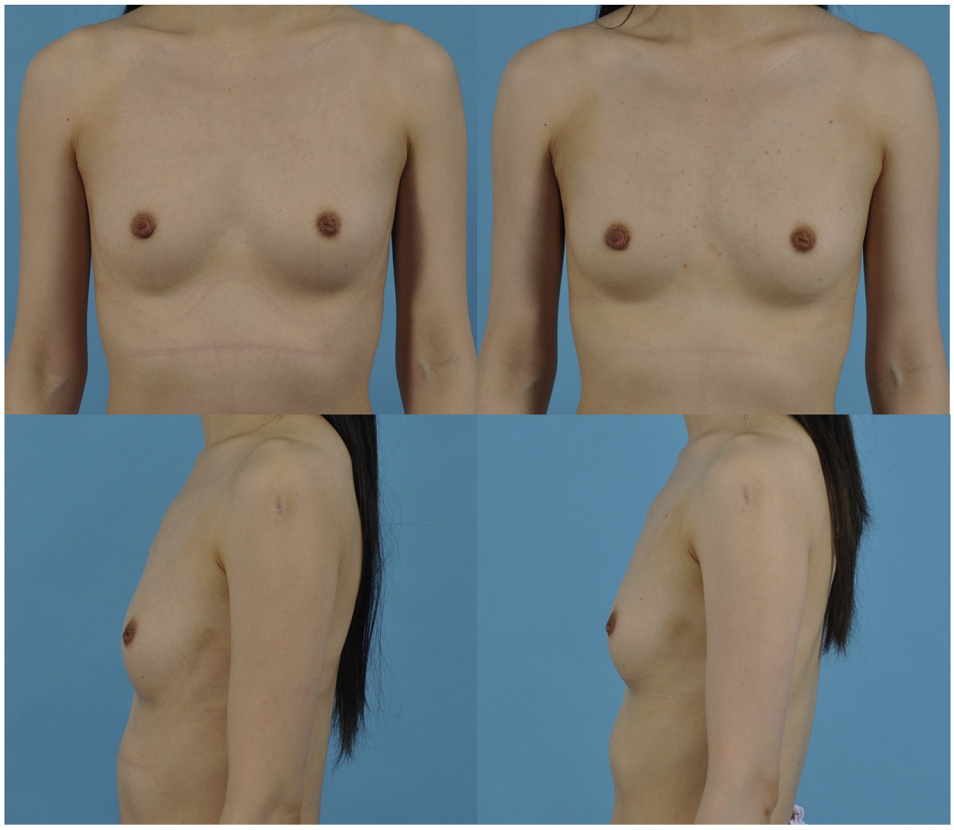

Figure 6 A 39-year-old woman before (left) and after (right) 12 weeks of EVERA use. After the treatment, dynamic contrast-enhanced magnetic resonance imaging vascular map analysis showed increased vessel count.

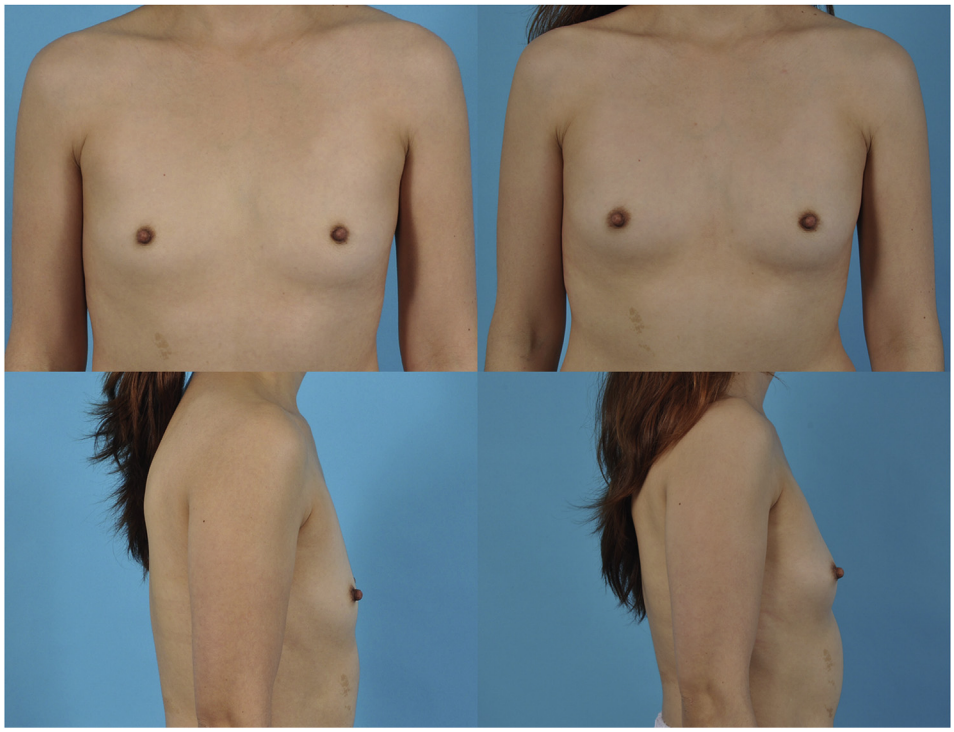

Figure 7 A 39-year-old woman before (left) and after (right) 12 weeks of EVERA use. Dynamic contrast-enhanced magnetic resonance imaging showed no significant difference in breast density before and after the application of the expansion device.

Table 3 Volume expansion results. Repeated-measures analysis of variance (RM-ANOVA) was used with statistical significance set to $p < 0.05$.

		AESTES group	EVERA group
		Mean (cc) ± SD	
Left	base	1029 ± 194	1229 ± 340
	8 weeks	1092 ± 205	1290 ± 373
	Volume increase	63	61
	p-value	0.011	0.152
	12weeks	1129 ± 224	1320 ± 366
	Volume increase	100	91
	p-value	0	0
	16weeks	1111 ± 220	1324 ± 372
	Volume increase	82	95
	p-value	0.003	0
Right	base	1143 ± 194	1282 ± 370
	8 weeks	1180 ± 216	1329 ± 379
	Volume increase	37	47
	p-value	0.007	0.03
	12weeks	1225 ± 222	1372 ± 386
	Volume increase	82	90
	p-value	0	0
	16weeks	1209 ± 220	1391 ± 374
	Volume increase	66	99
	p-value	0	0

Breast augmentation with a large amount of fat with external breast expansion has seen significant technical progress during the last two decades. The BRAVA device developed by Khouri and colleagues increased the upper limit of lipotransfer to over 300 cc,[9] and its safety and efficacy were confirmed in various clinical reports.[6,13] As surgeons continue to overcome technical difficulties such as fat necrosis or calcification and occurrence of cancer, lipotransfer is now considered one of the most effective breast augmentation options.

It has been generally believed that it is difficult to achieve adequate breast size increases with external expansion devices in patients with high breast density.[3] Hence, although the fat grafting technique could be a good alternative for Asian women who are very much afraid of having external scars, breast augmentation with large-volume fat transfer has been less popular in Asia than in Western countries. This study aimed to evaluate the efficacy of external expansion device application to breasts of Asian women. We also compared an external expansion device developed in Korea (EVERA), which was designed for patients with physical characteristics of a typical Asian woman — small body, narrow chest cage, highly dense mammary gland, low BMI, and small preoperative breast size — to a conventional American external expansion device (BRAVA). Additionally, by performing three-dimensional MRI studies throughout the trial, we recorded changes in breast vessel count and density to determine the effectiveness of external expansion as a pretreatment for subsequent fat grafting.

Previous studies analyzed breast volume changes with respect to BMI, whereas we attempted to quantify differences in density and vessel count in response to external expansion more objectively. The method of breast density measurement by semiautomatic segmentation proposed by Klifa et al.[14,15] was used to quantify fibroglandular tissue in the total breast volume, and vascularity quantification was performed by applying a 0—3-point scale developed by Martincich et al.[16] using contrast-enhanced MRI.

Failure of vascular ingrowth toward the transferred fat, a vital process in fat survival,[17,18] causes insufficient tissue oxygenation, ultimately leading to adipocyte necrosis and low survival of the grafted tissue.[19—21] Previous studies by Khouri et al. demonstrated that survival of transferred fat is higher in pre-expanded breasts than in breasts without pre-expansion and indicated that vessel count is an important factor for fat survival. The current trial revealed increases in the number and density of medium-sized blood vessels in the breast after applying external expansion. Although the relationship between vessel count and tissue oxygenation or wound healing was studied previously,[22,23] the link between survival of the grafted fat and vessel number or density has not been investigated. In an animal model, increased microvessel density was related to increased micro-graft survival.[24]

In this study, a laser scanner was used to measure more accurately changes in breast volume before and during the trial. Although laser scanning has not been widely employed in volumetric measurements in medical applications, a number of examples of its utilization can be found in facial and dental surgery[25,26] and medical photogrammetry.[27] Despite the objectiveness and accuracy of the results, the use of three-dimensional scanning for body volume measurements has not been validated, and this novel measurement tool requires calibration and validation, which will be performed in future studies.

After 12 weeks of external expansion, both left and right breast volumes significantly increased (by the mean values of 95 cc and 85 cc, respectively) compared with the baseline values. Although external expansion effectively increased breast volume in Asian women, the amount of the increase was much smaller than the amounts reported in previous studies by Schlenz et al. (155 cc) and Khouri et al. (306 ml) conducted in Caucasian patients. A probable reason for this result is that the duration of external expansion device application was longer in the previous studies (>18 weeks; range: 14—52 weeks in Schlenz et al.) than in our trial. Additionally, in the study by Khouri et al., the patients underwent large-volume fat transfer after 4 weeks of device application, and the additional expansion from the fat transfer could also have contributed to the larger increase. However, we believe that differences in breast characteristics such as baseline volume and cup size, as well as in BMI, between Asian and Caucasian women were most likely responsible for these results.[28] Thus, a breast volume increase of 80—90 cc may be considered substantial in smaller Asian women.

The primary shortcoming of this study is that menstrual periods of patients were not accounted for during monitoring of changes in breast density and vessel count. There have been many debates about changes in breast physiology over the menstrual cycle, and previously published studies[29,30] only reported increased blood flow observed by Doppler sonography. Nevertheless, the results would have been more precise if correlations could have been made

between the menstrual cycle and results of breast MRI measurements. However, as the present clinical trial was limited to 16 weeks, it was impossible to match the individual menstrual cycle of every patient. Future studies should attempt to minimize the effects of this bias. In addition, as mentioned above, the use of three-dimensional scanning for breast volume measurement has not been validated thus far, necessitating further validation studies. Lastly, the comparison of final results after fat transfer is not reported in the present study owing to scheduling and recruitment difficulties typical of prospective trials. The study mainly aimed to investigate the effects of external expansion as a pretreatment for adipose injection on breast parenchyma and vessel count. The results of fat transfer after expansion will be analyzed and reported in the near future.

Summary

Unlike Caucasian women, Asian women have small, highly dense breasts; narrow chest cages; and low BMI. This necessitates special approaches to breast augmentation in these populations. Breast augmentation with external expansion can both change the breast size and serve as a pretreatment that may potentially increase survival of the future fat graft. In the present trial, contrast-enhanced MRI revealed significant vascularization during external expansion. Moreover, breast volume was significantly increased by the expansion procedures in Asian women.

Acknowledgment

This study was supported by The Small and Medium Business Administration (SMBA) of Korean government. Consultations on medical statistics were provided by the medical research center of Seoul National University Bundang Hospital. Clinical Trial Registration: http://www.ClinicalTrials.gov, identifier number E1307-210-002.

References

1. Hackworth S. *ISAPS international survey on aesthetic/cosmetic procedures performed in 2011*. International Society of Aesthetic Plastic Surgery; 2012.
2. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007;**119**:775—85.
3. Del Vecchio DA, Bucky LP. Breast augmentation using pre-expansion and autologous fat transplantation: a clinical radiographic study. *Plast Reconstr Surg* 2011;**127**:2441—50.
4. Parrish JN, Metzinger SE. Autogenous fat grafting and breast augmentation: a review of the literature. *Aesthetic Surg J* 2010;**30**:549—56.
5. Rosing JH, Wong G, Wong MS, et al. Autologous fat grafting for primary breast augmentation: a systematic review. *Aesthetic Plast Surg* 2011;**35**:882—90.
6. Khouri RK, Khouri Jr RK, Rigotti G, et al. Aesthetic applications of brava-assisted megavolume fat grafting to the breasts: a 9-year, 476-patient, multicenter experience. *Plast Reconstr Surg* 2014;**133**:796—807.
7. Uda H, Sugawara Y, Sarukawa S, Sunaga A. Brava and autologous fat grafting for breast reconstruction after cancer surgery. *Plast Reconstr Surg* 2014;**133**:203—13.
8. Schlenz I, Kaider A. The Brava external tissue expander: is breast enlargement without surgery a reality? *Plast Reconstr Surg* 2007;**120**:1680—9. discussion 1690—1681.
9. Khouri RK, Rigotti G, Khouri Jr RK, et al. Tissue-engineered breast reconstruction with Brava-assisted fat grafting: a 7-year, 488-patient, multicenter experience. *Plast Reconstr Surg* 2015;**135**:643—58.
10. del Carmen MG, Halpern EF, Kopans DB, et al. Mammographic breast density and race. *Am J Roentgenol* 2007;**188**:1147—50.
11. Kim SJ, Kim M, Kim M-J. The affecting factors of breast anthropometry in Korean women. *Breastfeed Med* 2014;**9**:73—8.
12. White KK, Park SY, Kolonel LN, et al. Body size and breast cancer risk: the Multiethnic Cohort. *Int J Cancer* 2012;**131**:E705—16.
13. Khouri RK, Baker TJ. Initial experience with the Brava nonsurgical system of breast enhancement. *Plast Reconstr Surg* 2002;**110**:1595—8.
14. Klifa C, Carballido-Gamio J, Wilmes L, et al. Quantification of breast tissue index from MR data using fuzzy clustering. In: *Engineering in medicine and biology society, 2004. IEMBS'04. 26th Annual International Conference of the IEEE*. IEEE; 2004. p. 1667—70.
15. Klifa C, Carballido-Gamio J, Wilmes L, et al. Magnetic resonance imaging for secondary assessment of breast density in a high-risk cohort. *Magn Reson imaging* 2010;**28**:8—15.
16. Martincich L, Bertotto I, Montemurro F, et al. Variation of breast vascular maps on dynamic contrast-enhanced MRI after primary chemotherapy of locally advanced breast cancer. *Am J Roentgenol* 2011;**196**:1214—8.
17. Mashiko T, Yoshimura K. How does fat survive and remodel after grafting? *Clin Plast Surg* 2015;**42**:181—90.
18. Mineda K, Kuno S, Kato H, et al. Chronic inflammation and progressive calcification as a result of fat necrosis: the worst outcome in fat grafting. *Plast Reconstr Surg* 2014;**133**:1064—72.
19. Choi M, Small K, Levovitz C, et al. The volumetric analysis of fat graft survival in breast reconstruction. *Plast Reconstr Surg* 2013;**131**:185—91.
20. Karacaoglu E, Kizilkaya E, Cermik H, Zienowicz R. The role of recipient sites in fat-graft survival: experimental study. *Ann Plast Surg* 2005;**55**:63—8.
21. Sommer B, Sattler G. Current concepts of fat graft survival: histology of aspirated adipose tissue and review of the literature. *Dermatol Surg* 2000;**26**:1159—66.
22. Wijffels KI, Kaanders JH, Rijken PF, et al. Vascular architecture and hypoxic profiles in human head and neck squamous cell carcinomas. *Br J Cancer* 2000;**83**:674—83.
23. Taccone FS, Su F, De Deyne C, et al. Sepsis is associated with altered cerebral microcirculation and tissue hypoxia in experimental peritonitis. *Crit Care Med* 2014;**42**:e114—122.
24. Nishimura T, Hashimoto H, Nakanishi I, Furukawa M. Microvascular angiogenesis and apoptosis in the survival of free fat grafts. *Laryngoscope* 2000;**110**:1333—8.
25. Prado GR, Pereira M, Biló JR, et al. Stability of surgically assisted rapid palatal expansion a randomized trial. *J Dent Res* 2013;**92**:S49—54.
26. Ud-Din S, Bayat A. Non-invasive objective devices for monitoring the inflammatory, proliferative and remodelling phases of cutaneous wound healing and skin scarring. *Exp Dermatol* 2016;**25**(8):579—85.
27. D'Apuzzo N, Mitchell H. Medical applications. In: *Advances in photogrammetry, remote sensing and spatial Information sciences: 2008 ISPRS congress book*. London, UK: Taylor & Francis Group; 2008. p. 425—38.
28. Ramsey CR, Chase D, Scaperoth D, et al. Improved dose homogeneity to the intact breast using three-dimensional treatment planning: technical considerations. *Med Dosim* 2000;**25**:1—6.

29. Potten CS, Watson R, Williams G, et al. The effect of age and menstrual cycle upon proliferative activity of the normal human breast. *Br J Cancer* 1988;**58**:163.

30. Ramakrishnan R, Khan SA, Badve S. Morphological changes in breast tissue with menstrual cycle. *Mod Pathol* 2002;**15**: 1348–56.