Quantification of Left Atrial Appendage Spontaneous Echo Contrast in Patients With Chronic Nonvalvular Atrial Fibrillation

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Abstract

Objectives. The left atrial LA appendage is the most common site of thrombus formation in patients with atrial fibrillation, and integrated backscatter allows the quantitative assessment of LA spontaneous echo contrast SEC . Integrated backscatter was used to examine the significance of measuring appendage SEC, specifically in relation to echocardiographic variables implying thromboembolism, in patients with chronic nonvalvular atrial fibrillation.

Methods. Fifty-two patients with chronic nonvalvular atrial fibrillation and no prior anticoagulant therapy 35 men, 17 women, mean age 66 ± 7 years underwent transesophageal echocardiography with integrated backscatter analysis. The LA and LA appendage integrated backscatter intensity were measured with the regions of interest placed in the LA cavity and the appendage, respectively. The integrated backscatter intensity values for these two chambers corrected" LA" and" LA appendage" integrated backscatter intensity, respectively were corrected using values from the left ventricular cavity.

Results. The LA appendage integrated backscatter intensity values were available in 44 patients 85% . Overall, the corrected LA appendage integrated backscatter intensity was significantly increased compared with the corrected LA integrated backscatter intensity 2.8 ± 2.2 vs 2.0 ± 1.8 dB, p 0.001 . The corrected LA appendage integrated backscatter intensity was inversely correlated with the LA appendage velocity r 0.37, p 0.05 , but not with the LA dimension, appendage size, or left ventricular function. The corrected appendage integrated backscatter intensity 4.5 ± 2.3 vs 2.4 ± 1.9 dB, p 0.01 and LA integrated backscatter intensity 3.2 ± 2.1 vs 1.7 ± 1.7 dB, p 0.05 were higher in patients who had LA appendage thrombus n 8 than those who did not. With the corrected appendage integrated backscatter intensity set at 2.5 dB, the sensitivity for the presence of appendage thrombus was 88% and the specificity was 64%.

Conclusions. Patients with chronic nonvalvular atrial fibrillation had a denser SEC in the LA appendage compared with SEC in the main LA cavity. The severity of the appendage SEC was influenced by the LA appendage function rather than its size. Quantification of SEC in the appendage, rather than main LA cavity, was more valuable for assessing embolic potential.

J Cardiol 2001; 37 6 : 325 333

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INTRODUCTION

Spontaneous echo contrast SEC in the left atrial LA cavity appears as a" smoke-like" pattern caused by ultrasonic backscattering from erythrocyte aggregation, and is often detected by transesophageal echocardiography in patients with atrial fibrillation, mitral valve disease, or prior thromboembolism. The presence of SEC is associated with the development of LA thrombus and thromboembolic complications[1 4]. In patients with nonvalvular atrial fibrillation, the LA appendage is the most frequent site of thrombus formation[5 7], and depression of its function is significantly associated with the risk of thromboembolic events[6,8 10]. However, no data are currently available on the clinical relevance of appendage SEC, which is separately assessed from SEC in the main LA cavity.

Recently, new echo technology has developed integrated backscatter, which allows the quantitative assessment of SEC. In patients with atrial fibrillation or sinus rhythm, Klein *et al.*[11] and later others[12,13] demonstrated that the quantitative SEC value in the LA cavity was related to LA size, LA appendage velocity, LA thrombus, and hematological factors such as fibrinogen. This method also allows the quantification of appendage SEC by placing a region of interest in the appendage.

The present study used transesophageal echocardiography with integrated backscatter analysis in patients with chronic nonvalvular atrial fibrillation to examine the clinical significance of measuring appendage SEC, as related to echocardiographic variables that suggest the presence of thromboembolism.

METHODS

Patients

Fifty-two patients 35 men and 17 women, mean age 66 ± 7 years with chronic nonvalvular atrial fibrillation who underwent transesophageal echocardiography were enrolled in this study. Since all patients were referred for the evaluation of potential risks of thromboembolism, no patients had received any anticoagulant therapy. The diagnosis of chronic nonvalvular atrial fibrillation was based on the electrocardiographic and echocardiographic findings. Chronic atrial fibrillation was documented at two separate occasions by electrocardiography and there was no evidence of rheumatic changes in the mitral valve apparatus. The predom-

inant causes of atrial fibrillation were hypertensive heart disease n 13, dilated cardiomyopathy n 7, alcohol abuse n 2, hypertrophic cardiomyopathy n 1, left atrial septal defect n 1, calcified aortic stenosis n 1, and constrictive pericarditis n 1. The remaining 26 patients had lone atrial fibrillation no identifiable cardiac origin of atrial fibrillation. Four patients had a history of stroke.

Echocardiography

All patients gave informed consent to participate in the study before the induction of transesophageal echocardiography. Transthoracic echocardiography was performed immediately before transesophageal echocardiography. The left atrial dimension, left ventricular end-diastolic dimension, and left ventricular fractional shortening were determined using the standard M-mode criteria[14]. The severity of mitral regurgitation was semiquantitatively assessed using color-Doppler imaging[15].

Transesophageal echocardiography was performed using a 5-MHz omniplane transducer attached to a commercially available echocardiographic system SONOS 2500, Hewlett Packard, Inc. . Particular attention was paid to image the main LA cavity and LA appendage to assess the presence or absence of SEC and thrombus. SEC was identified as dynamic smoke-like echoes within the LA cavity, with a characteristic swirling motion distinct from white noise artifact, and was qualitatively graded as" none"," mild", and " severe", as described previously[1,16]. The distribution of SEC over the LA cavity including the appendage was also visually assessed. In many cases, there was dense SEC in the appendage and/or around its outlet compared with the other parts of the LA chamber. LA thrombus was defined as an echo-dense mass attached to the LA wall, and particular care was taken to differentiate thrombus from normal structures such as pectinate muscles.

LA appendage size and function were assessed using two-dimensional and Doppler echocardiography. In the longitudinal plane, the maximal LA appendage area was measured by planimetry. In the same plane, LA appendage emptying velocity was recorded with the pulsed-Doppler interrogation of the LA appendage orifice, and the highest LA appendage emptying velocity per cardiac cycle, usually at end-diastole, was averaged over 5 consecutive beats. Since filling velocities were approx-
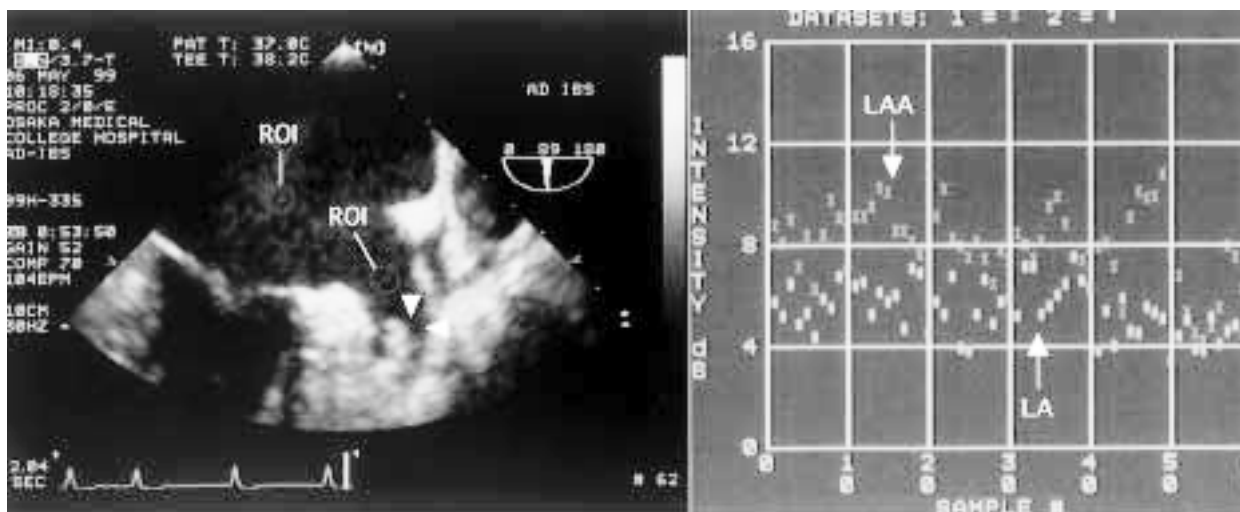
Fig. 1 Integrated backscattering images
    Left: Transesophageal echocardiography integrated backscattering image. The region of interest *circle* is placed in the main LA cavity, LA appendage, and left ventricular cavity. *Arrowheads* indicate thrombus.
    Right: Integrated backscattering curves for the LA cavity and LA appendage in a patient with spontaneous echo contrast.
    ROI   region of interest; LAA   left atrial appendage; LA   left atrium atrial .

imately equal in magnitude to the emptying velocities, they were not separately measured.

Analysis of integrated backscatter data

The SONOS 2500 echocardiography scanner includes an acoustic densitometry software program for integrated backscatter analysis. Transesophageal echocardiographic imagings were obtained showing the upper one- to two-thirds of the left ventricular cavity, the main LA cavity, and almost the whole LA appendage in one integrated backscatter image **Fig. 1** . For the quantitative assessment of SEC, the analysis system was configured to analyze 62 frames of integrated backscatter image data during a 2-sec period from cineloop memory, which had been digitally saved to an optical disk for subsequent analysis.

The time-gain-compensation and receive gain were adjusted such that optimal visualization of the integrated backscatter image was established[12] ; during the acquisition of integrated backscatter data, the smoothing filter for reducing noise in the time-intensity samples was preset to" off", and the lateral gain control was not used. The region of interest, a circle of 21 pixels, was placed in the main LA cavity, LA appendage, and left ventricular cavity **Fig. 1** . When tracking SEC over the LA cavity, the region of interest was placed on the most

intense SEC[11,12] . The integrated backscatter parameters obtained were values for the average image intensity mean integrated backscatter intensity and the peak-to-peak variability of the integrated backscatter signal in each region of interest, the former of which was used for analysis. Quantitative SEC values for the main LA cavity corrected LA integrated backscatter intensity and the LA appendage corrected LA appendage integrated backscatter intensity were corrected by the left ventricular integrated backscatter intensity values[11,12] . The display graph was preset to span the integrated backscatter intensity values in the range from 0 to 64 dB. Three sets of the cineloop were obtained and a median value adopted for each region of interest.

Reproducibility

Interobserver and intraobserver variabilities of integrated backscatter data were assessed in 10 patients by two independent observers S. M. and T. N. without knowledge of the presence or absence of LA thrombi or the patient's background.

Statistical analysis

Differences in echocardiographic parameters between patients with and without LA thrombus were analyzed using the unpaired *t*-test. The quanti-

Table 1   Echocardiographic data of the study patients

Variables		Range
M-mode, two-dimensional,		
and Doppler data（*n*＝52）		
LA dimension（cm）	4.9±0.6	4.8－0.6
LV diastolic dimension（cm）	5.2±0.8	3.9－7.7
LV fractional shortening（%）	29±9	10－43
Moderate to severe MR	2（4%）	
LAA velocity（cm/sec）（*n*＝51）	32±15	11－72
LAA size（cm²）	4.5±1.5	2.4－8.4
Qualitative SEC grade		
No SEC	26（50%）	
Mild SEC	21（40%）	
Severe SEC	5（10%）	
LA thrombus（%）	9（17%）	
IB data（*n*＝44）		
LV IB intensity（dB）	1.3±0.1	1.2－1.7
LA IB intensity（dB）	3.3±1.8	1.2－8.8
LAA IB intensity（dB）	4.0±2.2	1.2－9.4

Continuous values are mean±SD.
LV＝left ventricular; MR＝mitral regurgitation; SEC＝spontaneous echo contrast; IB＝integrated backscatter. Other abbreviation as in Fig. 1.

tative SEC values in the LA appendage vs main LA cavity within the same group were compared by paired *t*-test. Simple linear regression analysis was performed to evaluate the correlations between the quantitative SEC values and some echocardiographic parameters. Using a receiver operating characteristics curve[17], the best cutoff values were defined for the detection of LA thrombus. All data are expressed as mean±SD, and a *p* value＜0.05 was considered significant.

RESULTS

Echocardiographic data of the patients are listed in **Table 1**. Of the 52 patients, 26（50%）had SEC and 9（17%）had LA thrombus; no thrombus was observed in the main LA cavity. In 26 patients with SEC, 6 had SEC exclusively within the appendage cavity and around its outlet, and their qualitative SEC grade was all "mild". Six of the patients（23%）with SEC had LA thrombus. The underlying disorders in the nine patients with LA thrombus were hypertensive heart disease（*n*＝3）, dilated cardiomyopathy（*n*＝1）, alcohol abuse（*n*＝1）, hypertrophic cardiomyopathy（*n*＝1）, atrial septal defect（*n*＝1）, calcified aortic stenosis（*n*＝1）, and

constrictive pericarditis（*n*＝1）. Two patients had significant mitral regurgitation, and neither had SEC or thrombus.

The quantitative SEC value in the LA appendage was not available in eight patients for the following reasons: Almost complete obliteration of the appendage cavity due to vigorous appendage contraction（*n*＝4）; increased reverberation artifact（*e.g.*, reflection of the wall between the left upper lobe pulmonary vein and the LA appendage）（*n*＝3）; and large LA appendage thrombus occupying its cavity（*n*＝1）. Since all of these conditions precluded a region of interest kept constantly within the appendage cavity, the following analyses were performed on the remaining 44 patients（29 men and 15 women, mean age 66±7 years）.

Distribution of spontaneous echo contrast over the left atrial cavity

Overall, the corrected LA appendage integrated backscatter intensity was significantly increased compared with the corrected LA integrated backscatter intensity（2.8±2.2 vs 2.0±1.8 dB, *p*＜0.001; **Fig. 2**）, indicating that there was dense SEC in the LA appendage as compared with the main LA cavity.

Relationship between quantitative spontaneous echo contrast values and other echocardiographic variables

Table 2 shows a coefficient matrix of the correlation between corrected LA/LA appendage integrated backscatter intensity values and echo-Doppler parameters. There was a weak but significant correlation between the corrected appendage integrated backscatter intensity and appendage velocity; but no relationship was observed between the corrected appendage integrated backscatter intensity and LA dimension, appendage size, or left ventricular fractional shortening. Similar findings were observed for the corrected LA integrated backscatter intensity. The corrected LA appendage integrated backscatter intensity（4.5±2.3 vs 2.4±1.9 dB, *p*＜0.01）was higher in patients who had LA appendage thrombus than those who did not, as was the corrected LA integrated backscatter intensity（3.2±2.1 vs 1.7±1.7 dB, *p*＜0.05; **Fig. 3**）.
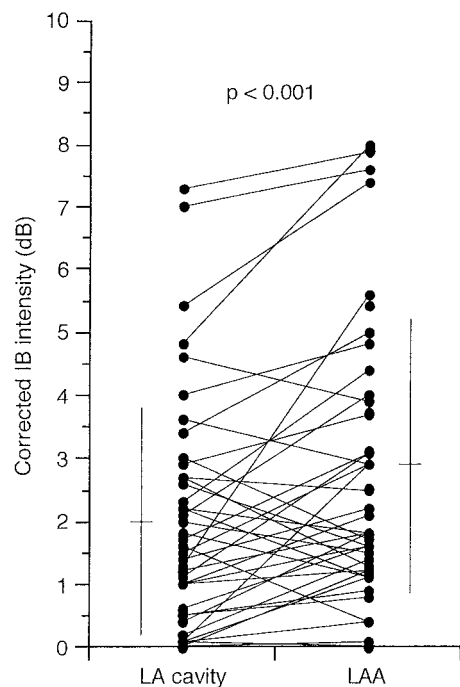
Fig. 2 Comparison of the corrected left atrial vs left atrial appendage integrated backscatter intensity values
Values are mean ± SD.
Abbreviations as in Fig. 1, Table 1.

Left atrial versus left atrial appendage spontaneous echo contrast for identifying left atrial appendage thrombus

According to the receiver operator characteristic curves for both corrected LA and LA appendage integrated backscatter intensity values **Fig. 4** , the latter had a larger area under the curve. The best cutoff point of the corrected appendage integrated backscatter intensity for the presence of appendage thrombus appeared to be between 2 and 3 dB. With the cutoff point set at 2.5 dB, for example, the sensitivity of LA appendage integrated backscatter intensity for the presence of appendage thrombus was 88% and the specificity was 64%.

Reproducibility

The mean differences of the interobserver variability for LA integrated backscatter intensity and LA appendage integrated backscatter intensity were 0.1 ± 0.1 dB range 0.0 0.1 and 0.4 ± 0.4 dB range 0.0 1.1 , respectively. Likewise, those of the intraobserver variability were 0.0 ± 0.0 dB range 0.0 0.1 and 0.5 ± 0.6 dB range 0.0 1.6 , respectively.

Table 2 Coefficient matrix for the correlations between quantitative spontaneous echo contrast values and other echocardiographic parameters

	Corrected LA IB intensity	Corrected LAA IB intensity
LA dimension	0.07	0.00
LV fractional shortening	0.11	0.18
LAA velocity	0.34	0.37
LAA size	0.08	0.09

p 0.05.
Abbreviations as in Fig. 1, Table 1.

DISCUSSION

Quantification of spontaneous echo contrast in the left atrial appendage

The present study demonstrated that the quantification of SEC in the LA appendage could identify patients at high risk for cardiogenic embolism. Although in some patients such quantification was impossible, those with good appendage function are unlikely to develop LA appendage thrombus. In this study, the corrected LA as well as LA appendage integrated backscatter intensity was related to the presence of LA thrombus, so the measurement of SEC in the main LA cavity does not necessarily lose its effectiveness for identifying high-risk patients. The main purpose of the present study was to examine the feasibility and clinical significance of measuring SEC in the appendage.

Blood stasis in the left atrial appendage

Although there have been numerous studies that describe LA SEC, little information is available on the distribution of SEC over the LA cavity. The only observation is that SEC develops in the LA appendage after successful cardioversion of atrial fibrillation in the situation called " atrial stunning "[18,19] . This study observed that the most common pattern of distribution of SEC is chiefly over the appendage cavity to its outlet ; our integrated backscatter data showed an increased LA appendage integrated backscatter intensity compared with LA integrated backscatter intensity. This finding also indicates that stagnation of blood is more likely to occur in the appendage than in the other atrial parts, further supporting the idea that the LA appendage is the most common site of
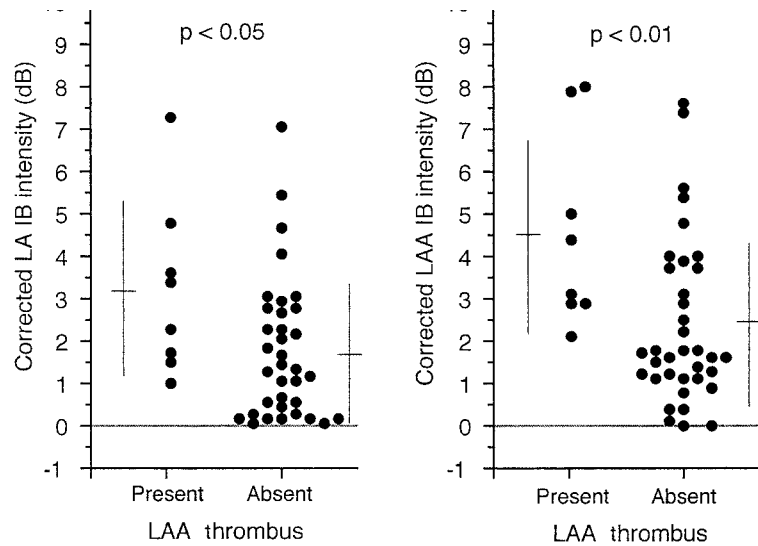
Fig. 3 Scatter plots of the comparison of the corrected left atrial and left atrial appendage integrated backscatter intensity values between patients with and without left atrial appendage thrombus
Values are mean ± SD.
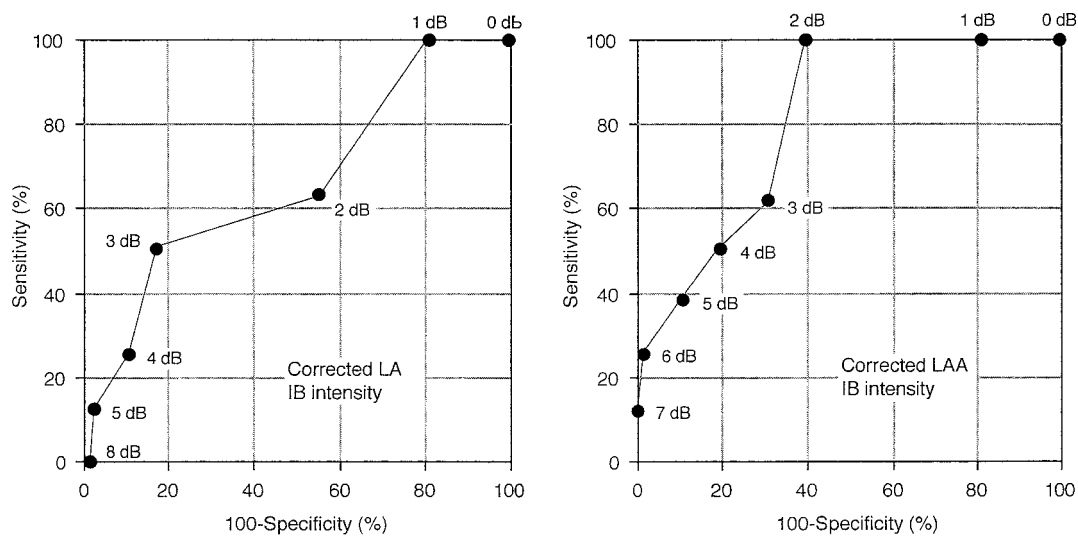Abbreviations as in Fig. 1, Table 1.

Fig. 4 Receiver operator characteristic curves for determining optimal sensitive and specific points of the corrected left atrial *left* and left atrial appendage *right* integrated backscatter intensity values related to the presence of left atrial appendage thrombus
Abbreviations as in Fig. 1, Table 1.

thrombus formation[5][7].

Localized LA blood stasis has been indirectly shown in previous studies that used trans-esophageal echocardiography. Kato *et al.*[20], for example, observed that the LA appendage was not opacified by intravenous contrast agent in atrial fibrillation patients with LA enlargement and poor appendage function. Furthermore, Shively *et al.*[21] demonstrated that in patients with atrial fibrillation or atrial flutter, blood velocity, assessed by pulsed-Doppler, was the lowest in the LA appendage and

the vicinity of the LA posterior wall, which was associated with the risk of stroke.

Relationship between left atrial appendage spontaneous echo contrast and cardiac function

In our study, the corrected LA appendage integrated backscatter intensity was correlated with the appendage velocity, but not with the LA or LA appendage size. This finding suggests that the functional status of the appendage is more important than its size in producing SEC. Reduced appendage

velocity is a marker of blood stasis[6,8   10] . Currently, the corrected LA appendage integrated backscatter intensity had no relationship with the LA size, which was not in concordance with the previous studies[11,12] . The absence of this relationship might be attributed to the relatively small number of patients or the differences in their characteristics. Although left ventricular dysfunction is considered to be one of the predictors of thromboembolism[22] , none of the previous studies found any correlation between left ventricular function and SEC[1,2,4] , as did the present study.

Clinical implications

One of the clinical goals is to find which group of patients with nonvalvular atrial fibrillation is at high risk for future thromboembolism. It is well known that SEC in the LA cavity is an important predictor of such complication in patients with atrial fibrillation[1   4] . In our study, the corrected LA appendage integrated backscatter intensity, as compared with the corrected LA integrated backscatter intensity, was a more sensitive and specific parameter for determining LA appendage thrombus. Given that appendage thrombus is the strong predictor of thromboembolism[23] , the measurement of appendage SEC could be a better method for identi-

fying high-risk patients and also an indication of specific antithrombotic therapy. Whether this index has any prognostic value, however, requires a large-scale prospective study.

Limitations

In the present study, only 2-sec integrated backscatter data were obtained for each region of interest, which is an inherent limitation in the currently available image acquisition system, although we acquired 3 sets of cineloops from each patient. Because of the small number of patients, the influence of quantifying appendage SEC on previous stroke was not assessed using multivariate analysis that includes other potential predictors of this risk.

CONCLUSIONS

We attempted to quantify LA appendage SEC in patients with chronic nonvalvular atrial fibrillation, and found that SEC in the LA appendage is denser compared with SEC in the main LA cavity. The severity of appendage SEC was influenced by appendage function rather than appendage size. Quantification of SEC in the appendage, rather than main LA cavity, was more valuable for assessing embolic potential.

Integrated Backscatter

:

integrated backscatter IB

:   52   35   17

66± 7   : Hewlett Packard   SONOS 2500

IB

IB   IB

:   IB   44   85%

2.8± 2.2 vs 2.0± 1.8 dB   *p*

0.001

r   0.37   *p*   0.05

4.5± 2.3 vs 2.4± 1.9 dB   *p*   0.01   3.2± 2.1 vs 1.7± 1.7 dB   *p*   0.05

8   2.5 dB

                                            88%   64%

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