Infective endocarditis (IE) is a disease still associated with high morbidity and mortality despite current treatments available. Embolic events (EEs) are a frequent and life-threatening complication that occurs in 13% to 49% of IE patients. The characteristic lesion of IE is vegetation, and 2-dimensional transesophageal echocardiography (2DTEE) plays an essential role in its diagnosis.

Previous studies have demonstrated that vegetation size is a predictor of EEs, and a maximum length of vegetation (MLV) ≥10 mm, measured with 2DTEE, has been proposed as a cut-off value for considering surgical treatment, although contradictory results have been reported.

During the past decade, real-time 3-dimensional transesophageal echocardiography (RT3DTEE) has been developed, which allows accurate quantitative and qualitative analysis of cardiac structures. With this technique, Asch et al showed an underestimation of the maximum diameter of intracardiac masses, including vegetations, when 2DTEE was used RT3DTEE could be useful in this context to overcome the inherent shortcoming of the 2DTEE method. To the best of our knowledge, there is a lack of published information regarding the association of vegetation size and EEs in IE as studied with this new technique.

Therefore, we hypothesized that RT3DTEE would reveal better estimation of MLV and thus might improve the risk assessment of EEs compared with 2DTEE.

Methods

Study Population

This is an observational and retrospective study of 60 patients with a definite diagnosis of IE by Duke criteria. These patients, who had both 2DTEE and RT3DTEE images of vegetations, were selected from the echocardiographic databases of Cedars-Sinai Heart Institute, Los Angeles, CA. The study was approved by the institutional review board of our center, and a waiver for informed consent was obtained.

Echocardiography

All echocardiographic studies were obtained using a Philips iE33 ultrasound system (Phillips Medical Systems, Andover, MA) during routine clinical practice in our Heart Institute with an X7-2t...
transesophageal transducer, and both 2DTEE and RT3DTEE complete studies were performed and digitally stored.

RT3DTEE data sets were separated from 2DTEE images, and both were analyzed blindly from each other with a minimum difference of 1 month between them. The RT3DTEE measurement of MLV was made with Advanced QLAB Quantification Software 8.1 (Philips Healthcare) by selecting the frame in which the vegetation was optimally visible (Figure 1A and 1B). After reviewing the entire morphology of the vegetation, MLV was measured by cropping the 3D volume with the appropriate 2D plane to obtain the largest value in each patient (Figure 2). For those with >1 vegetation, we selected the vegetation with the largest size.

The 2DTEE measurement of MLV was obtained with standard planes and their modified views to select the largest value for each patient as previously described.3

Information about the location of vegetations, whether the affected valve was native or prosthetic, shape and mobility of vegetations, valve regurgitation, leaflet perforation, and abscess formation was also collected.

Clinical Variables

For the purpose of this study, we selected EEs as the primary end point, defined as major arterial emboli with clinical manifestation or image confirmation. This clinical event was registered from medical records when it occurred within a week before echocardiographic images of vegetations were obtained or during hospitalization after echocardiographic diagnosis of vegetations due to IE.

Other relevant clinical information, including positive blood cultures and microorganism involved, heart failure symptoms, and inhospital mortality, was also collected from medical records.

Statistical Analysis

All continuous variable distributions met the normality assumption using the Kolmogorov–Smirnov test and were described by mean and SD. Categorical variables were expressed as frequencies and percentages. The paired t-test was used to compare the mean MLV between RT3DTEE and 2DTEE. Categorical variables were compared with χ2 test or Fisher exact test if application conditions were not fulfilled. A P value <0.05 was considered statistically significant for all comparisons.

Logistic regression models (backward stepwise method) were used to evaluate the association between MLV and occurrence of EEs after adjusting variables considered potentially relevant (P<0.20 in univariate analysis). Receiver operating characteristic curves and the estimation of area under the curve (AUC) were obtained for RT3DTEE and 2DTEE MLV measurements. A comparison of both AUCs was made with the DeLong method. Sensitivity, specificity, positive predictive value, and overall accuracy of different cut-off values were calculated for both techniques.

The intra- and interobserver reliability for MLV measured with RT3DTEE and 2DTEE was analyzed in a randomly selected sample of 30 patients from the whole population. For this purpose, 2-way mixed single-measure intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) were determined.
Statistical analysis was performed with IBM SPSS Statistics version 19 (SPSS Inc, Somers, NY).

## Results

We identified 60 patients with a definite diagnosis of IE and vegetation data by both 2DTEE and RT3DTEE. Demographic and baseline clinical characteristics as well as risk factors for IE are summarized in Table 1. The mean age of the population was 60.4±20.2 years, and 23 of them (38.3%) were women.

MLV as measured with RT3DTEE was 17.7±8.1 mm, with a minimum value of 2.9 mm and a maximum value of 44 mm. MLV as measured with 2DTEE was 14.5±6.4 mm, which was significantly lower than the RT3DTEE measurement, with a mean difference of 3.2 mm (95% CI, 2.1–4.2 mm; \( P < 0.00001 \); Figure 3).

There were no significant differences in vegetation size between native and prosthetic valves. No other clinical characteristics were found to be associated with vegetation size.

The presence of EEs was registered in 25 cases, which represents 41.7% of the study population, and from these EEs, 15 cases had cerebral embolism. EEs occurred before the echocardiographic study in 16 patients (64% of all EEs) and after the echocardiographic study in 9 patients (36% of all EEs). EEs were detected only by imaging tests in 4 cases (16% of all EEs). We established 2 groups of patients based on the presence or absence of major EEs. Both groups were well balanced for their characteristics. Women tended to be more frequently found in EEs group. However, this trend did not reach statistical significance (\( P = 0.066 \)).

We compared MLV as measured with RT3DTEE in patients in whom EEs occurred before the echocardiographic study (20.3±9.2 mm) with MLV of patients in whom EEs occurred after the echocardiographic study (22.1±7.4 mm). The difference between both groups was statistically nonsignificant (\( P = 0.612 \)).

Table 2 summarizes the RT3DTEE data from patients with IE. Most patients had 1 vegetation (86.7%), and the aortic valve was frequently involved (50%). Among the valves affected, 48 (80%) were native.

The prevalence of complications is reported in Table 3. In-hospital mortality occurred in 6 patients (10%), and shock of any type was present in 18.3%. The appearance of new severe valve regurgitation was detected in 56.7% of patients, but the presence of severe symptoms of heart failure (New York Heart Association class III–IV) occurred in only 10% of patients.

To determine the accuracy of MLV as measured with both techniques in patients with and without EEs, we calculated the receiver operating characteristic curves (Figure 4). The AUC was larger for RT3DTEE MLV (0.687) compared with 2DTEE MLV (0.642), although statistical significance was not reached (\( P = 0.18 \)). The best cut-off value for RT3DTEE MLV was 20 mm and for 2DTEE MLV was 16 mm.

For RT3DTEE MLV, the sensitivity and specificity of MLV \( \geq 20 \) mm were 60% and 77.1%, respectively, with a positive predictive value of 65.2%. The accuracy for correct classification with this cut-off value was 70%.

For 2DTEE MLV, the sensitivity and specificity of MLV \( \geq 16 \) mm were 52% and 74.3%, respectively, and a positive predictive value was 59.1%. The proportion of patients correctly classified with this cut-off value was 65%.

In a logistic regression analysis (Table 4), MLV was statistically associated with the occurrence of major EEs. In a univariable analysis, RT3DTEE MLV \( \geq 20 \) mm and mitral valve involvement were identified as predictors of EEs. The multivariable analysis indicated that both remained as predictors of EEs.

When 2DTEE MLV \( \geq 16 \) mm was used in the regression analysis, the same predictors of EEs were obtained. However, the adjusted odds ratio for 2DTEE MLV \( \geq 16 \) mm was 3.71

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**Table 1. Demographical and Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population (n=60)</th>
<th>Without Major EEs (n=35)</th>
<th>With Major EEs (n=25)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.4±20.2</td>
<td>61.8±20.6</td>
<td>58.4±19.9</td>
<td>0.522</td>
</tr>
<tr>
<td>Women</td>
<td>23 (38.3%)</td>
<td>10 (28.6%)</td>
<td>13 (52.2%)</td>
<td>0.066</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.1±5.6</td>
<td>25.5±5.3</td>
<td>24.6±6.0</td>
<td>0.550</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (55.0%)</td>
<td>22 (66.9%)</td>
<td>11 (44.0%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (23.3%)</td>
<td>8 (22.9%)</td>
<td>6 (24.0%)</td>
<td>0.918</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>31 (51.7%)</td>
<td>17 (48.6%)</td>
<td>14 (56.0%)</td>
<td>0.570</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17 (28.3%)</td>
<td>9 (25.7%)</td>
<td>8 (32.0%)</td>
<td>0.594</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>11 (18.3%)</td>
<td>7 (20.0%)</td>
<td>4 (16.0%)</td>
<td>0.748</td>
</tr>
<tr>
<td>Previous IE</td>
<td>6 (10.0%)</td>
<td>4 (11.4%)</td>
<td>2 (8.0%)</td>
<td>1</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>4 (6.7%)</td>
<td>1 (2.9%)</td>
<td>3 (12.0%)</td>
<td>0.298</td>
</tr>
<tr>
<td>Intracardiac prosthetic material</td>
<td>16 (26.7%)</td>
<td>11 (31.4%)</td>
<td>5 (20.0%)</td>
<td>0.324</td>
</tr>
<tr>
<td>Previous valve disease</td>
<td>26 (43.3%)</td>
<td>16 (45.7%)</td>
<td>10 (40.0%)</td>
<td>0.660</td>
</tr>
</tbody>
</table>

**EE** indicates embolic event; and **IE**, infective endocarditis.
(95% CI, 1.13–12.13), which was much smaller than that obtained for RT3DTEE MLV $\geq$20 mm.

There were no significant differences in these results when we excluded patients with prosthetic IE from the analysis.

Reliability Analysis of Measurements

For RT3DTEE MLV, there was excellent intraobserver reliability, with an ICC of 0.967 (95% CI, 0.932–0.984). The interobserver agreement was also good, with an ICC of 0.960 (95% CI, 0.918–0.981). For 2DTEE MLV, the intraobserver reliability showed an ICC of 0.843 (95% CI, 0.269–0.950), and interobserver reliability showed an ICC of 0.737 (95% CI, 0.034–0.915).

Discussion

This is the first study to demonstrate that 2DTEE, compared with RT3DTEE, underestimates the size of vegetations in patients with IE. Among several ways of measurements, we chose MLV for the purpose of establishing a direct comparison with 2DTEE, which has been a standard diagnostic technique in these patients and because MLV can be easily measured in clinical practice.

RT3DTEE allows the analysis of 3D volumes of cardiac structures in any possible 2D plane by cropping the images as required both online and offline whereas 2DTEE only shows a limited number of planes, possibly causing an underestimation of measurements, as suggested by a previous report. In this study, 17 patients with intracardiac masses were evaluated, but only 6 of them had vegetations due to IE. Our study is focused on this particular group of patients with a much larger sample.

Several 2DTEE studies have demonstrated morphological characteristics of vegetations, particularly the size of vegetation, as predictors of EEs. Few studies have reported contradictory results, which have been thought to be due to limitations regarding small sample size or the use of 2DTEE.

Value of RT3DTEE for Predicting the Risk of Embolism

In the receiver operating characteristic curves shown in Figure 4, we see the tendency for larger AUC when RT3DTEE was used, suggesting a potential improvement in overall accuracy. For predicting the occurrence of EEs, we found different best cut-off values for 2DTEE (16 mm) and RT3DTEE (20 mm). The cut-off value of 20 mm for RT3DTEE led to a relative increase in the overall accuracy of 8.3% in comparison with 2DTEE alone.

Other Predictors of Embolism in IE

The other predictor of EEs, as our study indicates, could be mitral valve involvement, which has been a controversial point in the literature. Cabell et al in a study of 145 patients with IE showed a higher risk for stroke if mitral valve were affected, but a larger study of Thuny et al found no association between mitral valve vegetation and EEs. In our analysis, we found mitral valve involvement to be an independent predictor of EEs. It should be noted, however, that the mitral valve is easier to image than the aortic valve using RT3DTEE, and there might be a bias toward mitral valve endocarditis in our study. Therefore, this point should be cautiously interpreted.

Some reports have identified an association between infecting organism and EEs. Thuny et al showed that *Staphylococcus aureus* and *Streptococcus bovis* were independently associated with EEs. This was not possible to be determined in our analysis because of the relatively smaller size of our sample. Moreover, this was beyond the scope of our study.

Previous studies have shown an association between vegetation size and mortality. Our study failed to prove this association probably because of the low prevalence of in-hospital mortality in our population (6; 10%) and because of the absence of follow-ups. Again, this was not the objective of the present analysis.

### Table 2. Real-Time 3-Dimensional Echocardiographic Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population (n=60)</th>
<th>Without Major EEs (n=35)</th>
<th>With Major EEs (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve involvement</td>
<td>25 (41.7%)</td>
<td>10 (28.6%)</td>
<td>15 (60.0%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Aortic valve involvement</td>
<td>30 (50.0%)</td>
<td>24 (68.6%)</td>
<td>6 (24.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Native valve</td>
<td>48 (80.0%)</td>
<td>27 (77.1%)</td>
<td>21 (84.0%)</td>
<td>0.513</td>
</tr>
<tr>
<td>MLV, mm</td>
<td>17.7±8.1</td>
<td>15.3±7.0</td>
<td>21.0±8.5</td>
<td>0.007</td>
</tr>
<tr>
<td>MLV $\geq$20 mm</td>
<td>23 (38.3%)</td>
<td>8 (22.9%)</td>
<td>15 (60.0%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

EE indicates embolic event; and MLV, maximum length of vegetation.

### Table 3. Complications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population (n=60)</th>
<th>Without Major EEs (n=35)</th>
<th>With Major EEs (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class III to IV</td>
<td>6 (10.0%)</td>
<td>5 (14.3%)</td>
<td>1 (4.0%)</td>
<td>0.386</td>
</tr>
<tr>
<td>New severe regurgitation</td>
<td>34 (56.7%)</td>
<td>19 (54.3%)</td>
<td>15 (60.0%)</td>
<td>0.660</td>
</tr>
<tr>
<td>Abscess</td>
<td>15 (25.0%)</td>
<td>9 (25.7%)</td>
<td>6 (24.0%)</td>
<td>0.880</td>
</tr>
<tr>
<td>Perforation</td>
<td>15 (25.0%)</td>
<td>8 (22.9%)</td>
<td>7 (28.0%)</td>
<td>0.650</td>
</tr>
<tr>
<td>Any type of shock</td>
<td>11 (18.3%)</td>
<td>8 (22.9%)</td>
<td>3 (12.0%)</td>
<td>0.332</td>
</tr>
<tr>
<td>ICU needed</td>
<td>20 (33.3%)</td>
<td>13 (37.1%)</td>
<td>7 (28.0%)</td>
<td>0.459</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6 (10.0%)</td>
<td>4 (11.4%)</td>
<td>2 (8.0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

EE indicates embolic event; ICU, intensive care unit; and NYHA, New York Heart Association.
Clinical Implications
Our study confirmed the underestimation in vegetation size in IE when only 2DTEE was used. This point had been only suggested by the previous report with small number of IE patients. Morphological assessment was incomplete with 2DTEE whereas RT3DTEE could show complex morphology and larger MLV than that obtained with 2DTEE. According to our study, RT3DTEE provided the entire morphology of the vegetation and determined its maximum size more accurately, leading to a better prediction of risk of embolism in IE patients. In addition, this analysis can be performed both online and offline in a matter of a few minutes.

RT3DTEE in clinical practice is performed along with 2DTEE, not separately, because the images can be obtained with the same transducer. Therefore, what our study suggests is that the use of RT3DTEE in combination with 2DTEE, in IE would lead to a better diagnosis without significant technical problems.

Study Limitations
There are few limitations in this study. The observational design and the fact that it was not an all-comer study would be the main limitations. Only patients with RT3DTEE data of vegetation were included, leading to a selection bias. However, in our Heart Institute, most of the patients with IE were systematically studied with RT3DTEE in the period of time analyzed in this study.

It is known that the size of vegetation may change after an EE. In our study there were not significant differences in MLV of vegetations between patients who had EEs after echocardiography and those who had EEs before echocardiography. Thus, we estimated the impact of the timing of the EEs to be the minimum in our echocardiographic results.

Other 3D imaging techniques with a better spatial resolution than RT3DTEE, such as MRI or CT, could be considered in the analysis of vegetations. However, because of the high mobility of the vegetation, which is often independent of the cardiac cycle, MRI and CT cannot show their complex structure in real time. There have been no reports in the literature on the use of other methodologies to demonstrate the dynamic change of vegetation with certainty. Only RT3DTEE can provide this unique information; thus, we had to compare it to 2DTEE directly.

In our study, patients with both native and prosthetic valve IE were included. The accuracy of measurement with RT3DTEE and its prognostic impact on vegetations attached

Table 4. Univariable and Multivariable Logistic Regression Analyses for Prediction of Major Embolic Events With Real-Time 3-Dimensional Transesophageal Echocardiography

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Women</td>
<td>2.71 (0.93–7.93)</td>
<td>0.066</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.46 (0.16–1.32)</td>
<td>0.148</td>
</tr>
<tr>
<td>Mitral valve involvement</td>
<td>3.75 (1.27–11.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>MLV ≥20 mm</td>
<td>5.06 (1.65–15.57)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; MLV, maximum length of vegetation; and OR, odds ratio.
to prosthetic material might differ compared with vegetations attached to native valves. No significant differences in clinical and echocardiographic characteristics were found between both groups, and valve condition, namely native or artificial, was not found to be a predictor of EEs. However, because of the small number of patients with prosthetic IE, our results should be cautiously interpreted in this particular group.

Another important limitation is the relatively small sample size (60 patients) compared with previous 2DTEE studies. However, the prevalence of EEs and other characteristics of our study population is in accordance with previous reports. It should be noted that RT3DTEE is a relatively new technique, and studies with higher number of patients should be conducted to confirm these important aspects.

Conclusions
RT3DTEE is a feasible and accurate technique for the analysis of vegetation morphology and size, leading to a better prediction of the embolism risk in these patients. Its combined use with 2DTEE can improve diagnosis accuracy and prognosis evaluation in IE.

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Disclosures
None.

References
Evaluation of Vegetation Size and Its Relationship With Embolism in Infective Endocarditis: A Real-Time 3-Dimensional Transesophageal Echocardiography Study
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