Mobile echoes on prosthetic valves are not reproducible

Results and clinical implications of a multicentre study

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Aims To test the hypothesis that inter-observer variability accounts for the wide variation in reported prevalences of fibrin strands on prosthetic heart valves and to develop criteria for their identification and reporting.

Methods and Results A videotape with 30 sequences of prosthetic heart valves imaged by transoesophageal echocardiography and showing abnormalities such as strands, microbubbles, and spontaneous echocardiographic contrast, was assessed in 13 European and three American centres. There were three duplicated examples, unbeknown to the observers. Definitions and reported prevalence rates of the abnormalities were analysed, and inter- and intra-observer agreement estimated with the kappa statistic.

Mobile echoes were identified in 40 to 80% of the sequences on the tape. The reported prevalence of mobile echoes correlated with the time spent reporting the tape. There was moderate inter-observer agreement for the identification of any mobile echoes (kappa=0.38), but no agreement for their labelling (kappa=0.22), in spite of similar definitions. Intra-observer reproducibility was good (agreement in 76% of the reduplicated sequences).

Conclusions The true prevalence and potential significance of mobile echoes on prosthetic heart valves cannot be assessed unless inter-observer consensus on echocardiographic criteria for identifying such echoes is reached.

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Key Words: Heart valve prostheses, observer variation, echocardiography, transoesophageal.

Introduction

Since thromboembolism remains a major complication of artificial heart valves, affecting up to 3% of patients per year[1], it would be valuable to identify markers of increased thromboembolic risk in recipients of prosthetic valves. Echocardiography is very useful in this context because it can detect abnormalities such as intra-cardiac thrombus, spontaneous echocardiographic contrast, and mobile linear echoes (also known as ‘fibrin strands’) on the prosthetic valve, or severe atheroma in the thoracic aorta, all of which have been shown to be associated with an increased embolic risk[2–8]. Some of these abnormalities are very subtle or transient, however, and their recognition may be difficult.

There is such wide variation in the reported prevalence of strands, ranging from 6 to 45%[2–8], that present it is extremely difficult to compare results between centres or to estimate the accuracy or clinical significance of reported associations. We considered that a major factor accounting for these differences may be inter-observer variability in diagnosis. We therefore designed a study to test inter-observer agreement for the detection of mobile echoes associated with prosthetic heart valves. We also assessed the diagnostic categories and definitions used in established echocardiographic centres for the identification of strands and of other mobile echoes.

Methods

Echocardiographic sequences were selected from transoesophageal studies performed in patients with
prosthetic heart valves. The majority of patients had been investigated as part of a prospective study of risk factors for embolism in patients with prosthetic heart valves; in this group, sequences were taken from a transoesophageal study performed within 2 h of cardiac surgery. A small number of patients with previously implanted prosthetic valves had been investigated for standard clinical indications; sequences were selected by one of the authors (A.A.I.) if the study revealed a good example of a particular abnormality. From the early postoperative group, some additional studies were included as examples of normal findings.

All the examinations were performed with a biplane or multiplane probe interfaced with a Hewlett-Packard Sonos 1500 echocardiographic machine. In the out-patient studies, patients received topical lidocaine and intravenous midazolam. Gain settings were kept relatively high in order to ensure demonstration of any spontaneous echocardiographic contrast or other subtle echocardiographic signs. All studies were recorded on S-VHS videotape.

The patients included were 13 men and 14 women, and their mean age was 65 (SD 11) years. The examples were chosen because in the opinion of the authors they included ‘strands’, microbubbles, mobile and immobile sutures, and spontaneous echocardiographic contrast. Some studies demonstrated more than one abnormality. No examples of proven major thrombosis or prosthetic infective endocarditis were included, and in the majority of patients the prosthetic valve had been implanted for too short a time for pannus to have developed.

The duration of the sequences ranged from 30 to 120 s (median 40 s). Three examples were duplicated, in order to allow assessment of intra-observer reproducibility. The duplicates were edited so that the start and the end-point was slightly different from that of the original sequence, and all information that might have contributed to their identification as duplicates (i.e. name of the patient, date of the echocardiogram) was masked out on the screen on all sequences. The 30 examples were edited in random order onto a videotape with a playing time of 15 min. A title before each clip displayed the position and type of prosthesis, but otherwise observers were blinded to the suspected findings and to the inclusion of three reduplicated studies. The position and types of prosthetic valves included on the tape are shown in Table 1.

### Table 1 Types and positions of valves imaged on the tape

<table>
<thead>
<tr>
<th></th>
<th>Tilting disc</th>
<th>Bileaflet</th>
<th>Biological</th>
<th>Caged ball</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic position</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Mitral position</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

Reporting the transoesophageal echocardiographic sequences

Twenty experienced cardiologists working in the field of echocardiography, and with special interest or expertise in valve disease, were approached and asked to participate in the study; 16 agreed (appendix). They were either members of the Working Group on Echocardiography of the European Society of Cardiology, or had previously published work on mobile echoes and/or prosthetic heart valves. Each reporting physician was asked to document his or her personal experience of transoesophageal echocardiography in patients with prosthetic heart valves, as well as the workload of the respective echocardiographic laboratory.

Participants were asked, before reviewing the videotape, to list the names which they use to describe mobile echoes associated with prosthetic heart valves, and to give a definition of each term. Each example was reported using a simple, semi-structured form, in which the physician had first to decide whether or not any mobile echoes were present, and then secondly to label each abnormality using the terms defined. Both ‘real-time’ and frame-by-frame review of the tape were recommended, and each physician was asked to document the time spent reporting the tape.

In our own centre, the videotape was prepared by one author (A.A.I.), and after an interval of some months reported ‘blind’ by another (A.G.F.). Results from this centre are included in the analysis. Subsequently the tape was reviewed in detail by both these authors jointly, in order to agree definitions (Table 2) and findings (Table 3 and Figs 1 and 2) which could then be used to compare results between all the participating centres.

The forms returned by the participating centres were first tabulated with regard to the presence or absence of mobile echoes. We included in our analysis the following categories of mobile echoes: strands, microbubbles, spontaneous echocardiographic contrast, thrombus/vegetation, and sutures. Very few centres used any other category; when other types of mobile echoes were identified, they were coded for the analysis of the prevalence of mobile echoes but not for the analysis of the specific types of echoes.

When coding was uncertain the reported results were matched according to the centre’s own definitions and were then included in one of the categories for analysis. Any individual examples that appeared ambiguous were reviewed jointly by two of the authors (A.A.I. and A.G.F.) and a consensus was reached. When reporting centres used a descriptive approach without allocating diagnostic labels, we coded ‘linear filamentous echoes’ as strands and ‘discontinuous, rapidly moving echoes’ as microbubbles.

On 10 (2%) of the total 480 pooled sequences the reporting physicians either suspected that there were mobile echoes but were not absolutely certain about their nature, or else they identified mobile echoes attached to the prosthetic valve but did not label them.
For the purpose of this analysis such instances were coded as strands; this approach may be justified by the low probability of thrombus or vegetations being present on prosthetic valves immediately after their implantation.

Mobile structures that were not related to the prosthetic valve were not coded in the analysis. Spontaneous echocardiographic contrast was not coded in a few instances because it was reported not to show any swirling motion, as required by the definition.

Table 2 Definitions used for reporting abnormal echoes associated with prosthetic valves

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands</td>
<td>Continuous linear, thin, mildly echogenic, mobile echoes. Often visible intermittently during the cardiac cycle, but recurring at the same site.</td>
</tr>
<tr>
<td>Microbubbles</td>
<td>Discontinuous stream of rounded, strongly echogenic, fast-moving, transient echoes occurring when there is motion of the occluder of the prosthetic valve.</td>
</tr>
<tr>
<td>Spontaneous echocardiographic contrast</td>
<td>Very small, diffuse, ‘smoke-like’ echoes with slow swirling motion.</td>
</tr>
<tr>
<td>Sutures</td>
<td>Linear, thick, bright, multiple, evenly spaced, usually immobile echoes consistently seen at the periphery of the sewing ring of a prosthetic valve; may be mobile when loose or unusually long.</td>
</tr>
<tr>
<td>Vegetation and thrombus</td>
<td>Cannot be distinguished by echocardiography alone; the differential diagnosis of any other sessile or pedunculated masses not fulfilling the above definitions depends on full clinical picture.</td>
</tr>
</tbody>
</table>

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Statistical methods

Inter-observer agreement was assessed using the multi-rater kappa statistic. Reporting centres were assessed by their sensitivity and specificity, against our own findings. Intra-observer agreement was assessed by calculating the proportion of the duplicated samples which were assessed in the same way on the two occasions.

Results

Experience of reporting centres

The experience of the reporting physicians and their respective centre’s transoesophageal echocardiographic workload are shown in Table 4. The reporting physicians spent between 25 and 135 min reporting the tape (mean (SD) 93 (31) min). There was a moderate positive correlation between the time spent reporting the tape and the prevalence of mobile echoes identified ($r=0.53$, $P<0.05$; mean prevalence 58%). There was no correlation between workload or experience and the time

Table 3 Prevalence of abnormalities identified on the tape in our centre

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Number of sequences</th>
<th>Percentage of sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mobile echoes</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>Strands</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>Microbubbles</td>
<td>14</td>
<td>47</td>
</tr>
<tr>
<td>Spontaneous echo contrast</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

Figure 1 (a) Transoesophageal echocardiographic appearance of microbubbles (small arrows) detected during closure of a single tilting-disc prosthetic mitral valve. The central strut of the prosthetic valve is also visible (large arrow). (b) Discrete, dot-like microbubbles (arrows) spreading along a linear trajectory into the left atrium during closure of a tilting-disc mitral prosthesis.
Comparison to our findings yielded an average sensitivity of 68%, and an average specificity of 85%.

Intra-observer consistency for the detection of any mobile echo was higher. Each centre assessed three replicated examples; of these 48 pairs there was consistency in 38 or 79% (95% CI (65, 87)), indicating good agreement. Three centres gave different responses in two out of the three pairs, and two centres identified two of the reduplicated sequences as such.

Definitions of mobile echoes

Descriptions of echoes compatible with strands were given by 15 of the 16 centres (Table 6). Strands were described as linear, filamentous or ‘filiform’ echoes by 11 of the centres, and as ‘thread-like’ or ‘frond-like’ by two centres. Synonyms used by the centres included ‘strands’ (eight centres), ‘fibrin strands’ (five centres), ‘soft tissue echoes’ and ‘filamentous echoes’ (one centre each); one centre provided no definitions. However, one centre defined strands as ‘non-linear’, and another identified them as being ‘thicker than threads or sutures’.

Only 50% of the centres reported microbubbles associated with the prosthetic heart valves. They were identified as being very echogenic, moving with high velocities, and having linear trajectories. One centre compared them with ‘champagne bubbles’.

The term ‘spontaneous echocardiographic contrast’ was utilized in this study by eight of the 16 centres. Swirling motion or smoke-like appearance were stated to be indicative of embolic risk, and gain dependence was noted. In two centres the term ‘echocardiographic contrast’ was applied both to the smoke-like appearance and to the small, bright, discontinuous echoes that we call microbubbles.

Thrombus and vegetations were recognized by 12 of the 16 centres which listed differentiating echocardiographic features, but there was consensus about the difficulty of distinguishing between the two in the absence of clinical information. Left atrial appendage thrombus was identified by five of the 16 centres on one of the sequences.

Definitions of echoes caused by sutures were offered by seven of the 16 centres. They were defined as arising always from the prosthetic valve ring. In two of these seven centres they were stated to be mobile, and in one centre they were described as ‘less mobile than

Table 4 Experience of reporting physicians and of their centres

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of TEEs per year per reporting physician</td>
<td>227 (126)</td>
<td>50–480</td>
</tr>
<tr>
<td>Percentage represented by prosthetic valves</td>
<td>21 (19)</td>
<td>5–75</td>
</tr>
<tr>
<td>Personal experience with TEE (years)</td>
<td>7 (2)</td>
<td>5–11</td>
</tr>
<tr>
<td>Number of TEEs per year in the reporting centres</td>
<td>708 (371)</td>
<td>150–1250</td>
</tr>
<tr>
<td>Percentage represented by prosthetic valves</td>
<td>16 (9)</td>
<td>5–40</td>
</tr>
</tbody>
</table>

TEE=transoesophageal echocardiography.
strands’. Other terms designating mobile echoes related to prosthetic heart valves but used by only one centre, included ‘pediculous echoes’, ‘intimal flap’ and ‘valvular residue’.

Specific diagnoses: inter-observer agreement

There is poor inter-observer agreement for the identification of various abnormal mobile echoes associated with prosthetic heart valves (Table 5). The kappa coefficient was low for strands in spite of generally similar definitions. The best agreement was seen for spontaneous echocardiographic contrast (kappa=0·56). Excluding the four centres that did not report either thrombus or vegetations, the inter-observer kappa coefficient for this combined category was 0·16.

Discussion

Many studies have found an association between the presence of strands on a prosthetic valve and cerebral embolic events, but the wide variation in reported prevalence (Table 6) suggests poor reproducibility for this diagnosis. The different characteristics of the populations studied might account for part of the variation, but the results of our study suggest that high inter-observer variability is the major factor. Since independent confirmation of the causes of mobile echoes associated with prosthetic valves is usually unobtainable, echocardiographic diagnosis will remain descriptive, and reproducible and non-overlapping criteria are important.

Table 5 Mean inter-observer agreement and range of reported prevalence of echocardiographic findings

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Prevalence range</th>
<th>Kappa coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strands</td>
<td>13–67%</td>
<td>0·21</td>
</tr>
<tr>
<td>Microbubbles</td>
<td>0–50%</td>
<td>0·22</td>
</tr>
<tr>
<td>SEC*</td>
<td>7–53%</td>
<td>0·56</td>
</tr>
<tr>
<td>Thrombus/vegetations</td>
<td>3–30%</td>
<td>0·16</td>
</tr>
<tr>
<td>Sutures</td>
<td>0–37%</td>
<td>0·08</td>
</tr>
<tr>
<td>Any mobile echo</td>
<td>27–80%</td>
<td>0·38</td>
</tr>
</tbody>
</table>

*Spontaneous echocardiographic contrast.

Figure 3 Reported prevalences of mobile echoes (●) and of strands (□). Centers have been arranged in the ascending order of prevalence of strands.

Mobile, linear, filamentous echoes were described on native valves in 1991[9] and on prosthetic valves in 1992[6], when they were dubbed ‘fibrin strands’. This label stuck and it is currently widely used. Evidence from operated patients is conflicting, however, since direct inspection has both confirmed[8] and refuted[5] prior transoesophageal echocardiographic findings of filamentous structures. They have been noted to resolve during successful thrombolysis of a thrombosed mitral prosthesis[10], suggesting that they may indeed be composed of fibrin, but until more evidence as to aetiology is available, we recommend the purely descriptive term ‘strands’.

In all centres participating in this study apart from one, strands accounted for the majority of mobile echoes identified (see Fig. 3), and most centres described them as mobile linear structures. Nonetheless, the kappa statistic for inter-observer agreement on strands was only 0·21, indicating poor reproducibility. Good agreement on definitions did not translate into clinically useful consensus on diagnosis.

The echocardiographic examples selected for this study were mostly obtained within 2 h of surgery. This implies that strands can form very soon after valve replacement, perhaps due to low levels of anticoagulation at this time[7]. Further investigations are warranted.
to explore the relationship between these findings and the risk of peri-operative neurological complications.

Microbubbles

‘Microbubbles’ are bright, short-lasting, fast-moving and discrete echoes associated with prosthetic valve closure. The exact mechanism for their appearance is unknown, but cavitation has been proposed\[11\]. Their significance is also unclear, although they have been linked to haemolysis, and in vitro cavitation has been shown to damage the surfaces of prosthetic valves\[12\]. There is also evidence connecting the presence of microbubbles to the detection of high intensity transient signals on transcranial Doppler monitoring\[13\]. In a study of 138 patients with mechanical left-sided heart valves, transoesophageal echocardiography revealed microbubbles in 35% and more frequently in the mitral than in the aortic position\[14\].

The participating centres reported microbubbles on the tape less frequently than they reported strands. It is possible that physicians do not report microbubbles routinely if they consider their transient appearance to be insignificant. Some participants called these appearances ‘contrast’, illustrating the difficulty of comparing findings from different centres when there is no consensus on terminology. Even with standardized criteria, however, it may be very difficult to distinguish microbubbles from strands (as was demonstrated in some of the examples on our videotape). Both are seen as small mobile echoes, and microbubbles sometimes appear repeatedly at the same location on the prosthetic valve and at the same time during successive cardiac cycles, just like strands. In our experience, frame-by-frame review of the videotape or cine-loop helps to differentiate between them: microbubbles are discontinuous, dot-like echoes (although ‘acoustic smearing’ may occur, making them look somewhat linear) which move fast away from the valve and are visible for only a few frames after the closure of the occluder, whereas strands are continuous and thread-like echoes which do not move away from the prosthesis and which are usually visible for a longer time in each cardiac cycle than microbubbles.

Spontaneous echocardiographic contrast

Spontaneous echocardiographic contrast has a smoke-like appearance with a swirling pattern of motion, and it is seen in areas where the velocity of blood flow is low. Its mechanism remains controversial; there is experimental evidence that red cell aggregates cause spontaneous echocardiographic contrast\[15\], although this has been questioned.

Our results show that some physicians consider microbubbles to be a sub-type of spontaneous echocardiographic contrast. This is in keeping with the suggestions of an expert panel of the American Society for Artificial Organs\[16\] which distinguishes between two phenomena under this heading: high intensity, smoke-like spontaneous echocardiographic contrast, associated with stasis and embolic risk, and microbubble-like signals which are either small gas bubbles or particulates that can be detected by transcranial Doppler monitoring in the cerebral circulation. To complicate the matter further, there are reports that distinguish several types of high-intensity spontaneous echocardiographic contrast\[17\].

In this study the inter-observer agreement for the identification of high intensity, smoke-like spontaneous echocardiographic contrast was acceptable. In recently reported trials, two observers concurred in identifying spontaneous echocardiographic contrast in 97% of cases\[18\] and the kappa statistic for inter-observer agreement was 0·56\[19\] respectively.

Thrombus and vegetations

The likelihood of thrombus or vegetation being present on a prosthetic valve immediately after implantation was deemed to be small, and in our centre none of the
sequences was interpreted as showing these abnormalities. Most centres commented on the impossibility of making this diagnosis on echocardiographic grounds only.

**Sutures**

We are not aware of published data about the echocardiographic appearance of sutures on prosthetic valves. Most of the centres that offered definitions for sutures, including ourselves, described them as immobile structures on the valve ring, but two centres described them as mobile. In our experience, only dehisced sutures are mobile.

**Clinical implications**

Our results show that it is very difficult to obtain interobserver agreement for the labelling of mobile echoes on prosthetic valves when no clinical information is available. In practice, the clinical context in which an abnormality is identified will influence the significance attached to it, and repeated echocardiograms are frequently needed to clarify the nature of such abnormalities. For example, mobile nodular echoes may be identified as thrombus in a patient with poorly controlled anticoagulation, or as vegetation in a febrile patient, although their echocardiographic appearance may be identical.

**Limitations of this study**

There is no independent standard against which the findings reported in this study could be compared, nor is a standard likely to be developed as long as there is no in vitro model of strands, no independent diagnostic test to confirm their presence and no irrefutable proof of their composition and histological structure. For the purposes of conducting an analysis, we therefore compared the findings reported in the other centres with our own. By chance, and unaware of the results from other centres, we had reported the highest prevalence of mobile echoes, so it was not inappropriate to assess the sensitivity of the other centres against our findings. We recognize that this is an arbitrary benchmark, however, and that other criteria or definitions could also have been used. Since the study was not designed to provide absolute results, the compromises which were required for analysis do not detract from the finding that there is very marked variability in reporting these abnormalities.

We wanted to assess the diagnostic labels that established centres use, without prompting, and so we used open-ended questions. This meant that the reports were difficult to code and some ‘pooling’ of diagnostic categories was unavoidable. Also, the analysis did not allow for the coding of each interpreter’s confidence in making each diagnosis. It is possible that reproducibility would have been better if analysis had been restricted only to confident diagnoses, or if longer sequences had been included on the videotape. In five instances in three centres (1% of the total of 480 reported sequences) the sequences were not reported because gain settings were identified to be too high. These had been used deliberately, to ensure that transient mobile echoes that were only mildly echogenic were not missed. Another problem is that it is impossible to be certain that different physicians were referring to the same abnormality when they used the same label for a particular echocardiographic sequence.

There is a loss of image quality when echocardiographic images are recorded on video tape, and the copying process decreases the quality further. Ideally, the digital format should be used for inter-centre comparisons of reporting practices. However, this format is not yet widely available; moreover, all the published literature on strands and other mobile echoes on prosthetic valves is based on the use of video recordings, so our results are representative for the current set-up of echocardiographic laboratories.

**Conclusions**

There is lack of consensus among experienced physicians in the identification and labelling of mobile echoes associated with prosthetic heart valves, in spite of generally similar definitions. Consensus on diagnostic criteria is necessary before further attempts should be made at characterizing these echoes and at establishing their clinical significance.

**References**


Appendix

Participating physicians and centres

Eduard Apetrei National Heart Institute, Bucharest, Romania; Helmut Baumgartner University Hospital, Vienna, Austria; Bertrand Cormier Tenon Hospital, Paris, France; Mark A. de Belder South Cleveland Hospital, Cleveland, U.K.; Pierre Decoode University Hospital, Bruxelles, Belgium; Karl Dennig German Heart Center, Munich, Germany; Frank Flachskampf RWTH Hospital, Aachen, Germany; Alan G. Fraser University Hospital of Wales, Cardiff, U.K.; Thomas Menzel University Hospital, Mainz, Germany; Suzanne Mohr-Kahaly University Hospital, Mainz, Germany; Navin C. Nanda University of Alabama, Birmingham, U.S.A.; Luc A. Pierard University Hospital, Liege, Belgium; Raymond Roudaut Cardiology Hospital, Haut-Leveque, France; Pravin M. Shah University Medical Center, Loma Linda, U.S.A.; George R. Sutherland Western General Hospital, Edinburgh, U.K.; Paul A. Tunick New York University Medical Center, New York, U.S.A.; Bengt Wranne Linkoping Heart Center, Linkoping, Sweden.