Early Operation in Patients With Mitral Valve Infective Endocarditis and Acute Stroke Is Safe



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Background. To determine if preoperative embolic stroke is associated with an increased risk of post-operative stroke among patients undergoing early operation for mitral valve (MV) infective endocarditis (IE), we compared outcomes among patients presenting with and without acute stroke.

Methods. From 2003 to 2015, 243 consecutive patients underwent surgery for active MV IE. Patients were categorized into 2 groups: 72% (174 of 243 patients) with no preoperative acute stroke (clinical, radiographic or both) and 28% (69 of 243 patients) with stroke. Both preoperative and postoperative strokes were confirmed in all patients with brain computed tomography or magnetic resonance imaging and comprehensive examination by a neurologist.

Results. Among patients presenting with stroke, 33% (23 of 69 patients) were asymptomatic and had only positive imaging findings. The median time from

Infective endocarditis (IE) is the indication for operation in 5% of patients having mitral valve (MV) surgery in the United States [1]. The incidence of IE has remained high and despite introduction of new generation of antibiotics and aggressive surgical intervention, the in-hospital mortality rate is between 20% and 30% [2–4].

Neurologic complications in patients presenting with MV IE are the most common extracardiac complications of IE [5]. Clinical stroke is diagnosed in 25% to 30% of patients with MV IE [4]. There is evidence of acute brain embolism as many as 50% of patients presenting with MV IE undergoing preoperative computed tomography (CT) scan [6]. The presence of embolic cerebral injury in patients with MV IE makes management challenging, particularly when indications for operation are present. Current guidelines recommend delaying MV surgery for at least 4 weeks from the time of stroke (Class IIa, level of

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admission to operation was 5 days. The overall rate of new postoperative stroke was 4% (10 of 243 patients). The rate of postoperative stroke was not different between the 2 groups: 4% (7 of 174 patients) among patients with no preoperative stroke and 4% (3 of 69 patients) with stroke (p=0.9). One patient developed a hemorrhagic conversion of an acute infarct. Operative mortality was 7% (13 of 174 patients) among patients with no preoperative stroke and 7% (5 of 69 patients) among patients with stroke (p=0.9).

Conclusions. MV surgery for IE and acute stroke can be performed early with a low risk of postoperative neurologic complications. When indicated, surgical intervention for MV IE complicated by acute stroke should not be delayed.

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evidence C) [7]. The rationale behind delaying operation is that the blood-brain barrier is disrupted in an ischemic area, and therefore the risk of bleeding with anticoagulation or blood pressure variation is increased. Cerebral vascular autoregulation is dysfunctional and patients are predisposed to blood extravasation [8]. Furthermore, the ischemic area can expand with hypoperfusion during cardiopulmonary bypass [8-10]. Although greatly feared, hemorrhagic conversion of an ischemic embolic lesion in the setting of IE has been found to be rare [6, 11, 12], with reported rates between 0% and 2% [4, 6, 13]. Delaying operation to allow resolution of cerebral injury and decrease the risk of worsening neurologic deficit or hemorrhagic conversion may have adverse consequences including further valve destruction, lower rates of valve repair, repeat embolization, worsening of sepsis, and progressive worsening of heart failure. Our institutional approach to the treatment of patients with MV IE has been aggressive and early operative intervention, with delays warranted only for uncontrolled sepsis, brain injury with a large volume of intracerebral blood, or neurologic devastation [6]. The aim of this study was to evaluate the outcomes of early MV operation for IE among patients with preoperative neurologic injury compared with patients with no evidence of preoperative neurologic complications.

Material and Methods

Between January 2003 and March 2015, 314 consecutive patients underwent operation for MV IE at the University of Maryland Medical Center. Patients who had treated IE (n = 71) were excluded, leaving 243 patients for analysis. If the patient was receiving antibiotics for IE at the time of surgery the disease was considered active. If no antibiotic medication was given at the time of operation other than prophylactic medications, then the infection was considered treated. The institutional review board of the University of Maryland Medical Center (HP-00040773) approved this retrospective study and patient consent was waived. Patient data were gathered through the local Society of Thoracic Surgeons Database and chart review.

The diagnosis of IE in all patients was determined based on the established criteria [14]. Preoperative transesophageal echocardiography was performed in all patients to determine characteristics of the vegetation, the degree of mitral regurgitation (MR), the involvement of other valves or the presence of an abscess. As part of the workup, patients routinely underwent head, chest, and abdominal CT scan before operation. We defined stroke based on the Stroke Council of the American Heart Association/American Stroke Association as any brain, spinal cord, or retinal cell death attributed to ischemia, based on neurological exam, neuroimaging, or evidence of primary injury [15]. Patients with neurologic signs or symptoms or any evidence of stroke on imaging were fully examined by a neurologist. Acute stroke was defined as radiographic evidence of stroke or clinical neurologic dysfunction [15]. Patients were categorized into 2 groups based on the presence or absence of stroke. Indication for operation included the presence of any of the following: severe MR, mobile vegetation, or vegetation size greater than 10 mm [16]. Operation was scheduled electively as soon as possible after preoperative workup was complete. Operation was delayed or not pursued if the patient had coma or uncontrolled sepsis, or if a large volume (>1 to 2 cm²) of intracerebral blood was present on neuroimaging. Postoperative outcomes including the rate of permanent stroke and operative mortality were compared between the 2 groups. Long-term mortality data were collected from the Social Security Death Index and supplemented by direct contact with patient's physicians and directly with patients and families.

Statistical Analyses

Analyses were conducted using statistical software (JMP 8.0, SAS Institute, Cary, NC). Values are presented as mean \pm SD or median with first and third quartiles. Median values were used when the data had skewed distributions. We used t tests and chi-square tests to compare the perioperative outcomes between the 2 groups. Kaplan-Meier survival estimates were calculated for each group and compared using the log-rank test. For all analysis, a p value less than 0.05 in a 2-sided test was considered statistically significant.

Results

Patient Characteristics

Of 314 patients who underwent MV surgery for IE, 243 (77%) patients had active IE and were included in the study. Seventy-two percent (174 of 243 patients) had no clinical or radiographic evidence of stroke whereas 28% (69 of 243 patients) were diagnosed with preoperative acute stroke. Among patients diagnosed with stroke, 67% (46 of 69 patients) had findings on clinical examination consistent with stroke, whereas the remaining 23% (23 of 69 patients) had imaging evidence of brain infarction or hemorrhage with no clinical findings. Overall, preoperative brain imaging was performed in 91% (221 of 243 patients).

The mean age of patients was 50 ± 14 years (range, 18 to 83 years) and 65% (157 of 243 patients) were men (Table 1). Thirty percent (72 of 243 patients) had a history of intravenous drug abuse. The possible identified underlying causes of IE among nonintravenous drug abusers were hemodialysis catheter infection (n = 42), cellulitis or osteomyelitis (n = 11), infected port catheter or total parenteral nutrition line (n = 9), gastrointestinal or urinary tract infection (n = 11), immunosuppression (n = 7), recent Lyme disease (n = 3), dental abscess or infection or intervention (n = 6), and history of MV prolapse (n = 15). The possible underlying cause of IE was not identified in 67 patients.

Concomitant tricuspid valve IE was present in 14% (34) of 243 patients) and aortic valve IE was present in 30% (74 of 243 patients). There were no significant differences in the rates of preoperative comorbidities between the 2 groups. A history of prior stroke was present in 12% (28 of 243 patients) and 24% (58 of 243 patients) had dialysisdependent renal failure. Atrial fibrillation was present in 15% (38 of 243 patients). Eighteen percent (44 of 243 patients) had prior cardiac operations. Prosthetic MV IE was present in 16% (38 of 243 patients).

The most common organism was Staphylococcus aureus in 42% (101 of 243 patients) (Table 2). The causative organism was not significantly different between the 2 groups.

Preoperative neurologic symptoms among the 46 patients with preoperative clinical stroke included unilateral extremity weakness (n = 19), altered mental status (n = 14), aphasia (n = 9), headache (n = 1), hemineglect (n = 1), seizure (n = 1), or visual disturbances (n = 1). Thirty-three percent (23 of 69 patients) of patients had no neurologic symptoms. Among patients with preoperative acute stroke, preoperative head CT or magnetic resonance imaging scan showed positive findings in 98% (67 of 69 patients). The most common findings included acute embolic stroke in 64%, embolic stroke with hemorrhage in 20%, hemorrhage in 5%, abscess with infarct in 2%, abscess with hemorrhage in 2%, mycotic aneurysm with infarct and hemorrhage in 2%, and mycotic aneurysm alone in 2% (Table 3). The 2 patients with negative

Table 1. Patient Characteristics

Variable	Overall $(N = 243)$	No Preoperative Stroke $(n = 174)$	Preoperative Stroke $(n = 69)$	p Value
Age, years	50 ± 14	51 ± 14	49 ± 15	0.2
Male	157 (65)	115 (66)	42 (60)	0.4
Ejection fraction, %	56 ± 12	56 ± 13	55 ± 10	0.5
History of myocardial infarction	30 (12)	22 (13)	8 (11)	0.8
History of atrial fibrillation	38 (15)	28 (16)	10 (14)	0.8
Hemodialysis	58 (24)	43 (24)	15 (22)	0.7
Intravenous drug abuse	75 (31)	49 (28)	26 (38)	0.1
Previous cardiac surgery	44 (18)	37 (21)	7 (10)	0.04
Previous mitral valve operation	38 (16)	31 (18)	7 (10)	0.17
Repair	13 (5)	10 (6)	3 (4)	0.3
Replacement	25 (11)	21 (12)	4 (6)	0.5

Values are mean \pm SD or n (%).

neurological imaging presented with expressive aphasia and a neurologist confirmed stroke.

Operative Characteristics

The median time from admission to our hospital to operation was 5 days among patients with no preoperative acute stroke (interquartile range, 2 to 8 days) and 6 days with stroke (interquartile range, 3 to 9 days; p = 0.08). Only 8 patients with preoperative acute stroke underwent MV operation more than 2 weeks after admission. MV repair was successful in 55% (112 of 207 patients) of patients with no history of prior MV operation. Among patients with staphylococcal IE, the repair rate was lower compared with other organisms, although it was not statistically significant (43% versus 51%; p = 0.2). Concomitant cardiac surgical interventions are summarized in Table 4. Of 25 patients with history of prior MV replacement, 15 patients had bioprosthetic valve IE (involvement of tissue leaflets, infection of the swing ring) and 10 patients had mechanical MV IE (involvement of the swing ring, dehiscence).

Perioperative Outcomes

Operative mortality for the entire cohort (in-hospital or within 30 days of discharge) was 7% (18 of 243 patients).

Operative mortality was 7% (13 of 174 patients) among patients with no preoperative stroke and 7% (5 of 69 patients) among patients with preoperative acute stroke (p = 0.9). Operative mortality was 4% (6 of 145 patients) among patients who underwent isolated primary MV operation (4% [4 of 105 patients] in the no preoperative stroke group, 5% [2 of 40 patients] in preoperative stroke group; p = 0.3). Causes of death were multisystem organ failure (n = 6), inability to wean from cardiopulmonary bypass and severe pulmonary hemorrhage (n = 2), ischemic bowel (n = 3), vasodilatory shock and cardiac arrest (n = 6), and intracranial hemorrhage (n = 1).

Postoperative morbidities were not significantly different between the 2 groups (Table 5).

Neurologic Outcomes and Survival

Postoperative new permanent stroke was documented in 4% (10 of 243 patients). The rate of postoperative stroke was identical in the 2 groups: 4% (7 of 174 patients) among patients with no preoperative acute stroke and 4%(3 of 69 patients) among patients with preoperative acute stroke (p = 0.9) (Fig 1). Only 1 (1%) patient among the entire group of patients with preoperative stroke developed hemorrhagic conversion at the site of a preoperative

Table 2. Causative Microbial Pathogens

Organism	Overall $(N = 243)$	No Preoperative Stroke $(n = 174)$	With Preoperative Stroke $(n = 69)$	p Value
Staphylococcus	114 (47)	77 (44)	37 (54)	0.24
S. aureus	101 (42)	68 (39)	33 (48)	
S. epidermidis	5 (2)	3 (2)	2 (3)	
Coagulase negative	8 (3)	6 (3)	2 (3)	
Streptococcus species	57 (23)	41 (24)	16 (23)	0.9
Enterococcus faecalis	19 (8)	16 (9)	3 (4)	0.3
Candida	4 (1)	3 (2)	1 (1)	0.9
Culture negative	35 (15)	29 (17)	6 (9)	0.1
Others	14 (6)	8 (5)	6 (9)	0.7

Values are n (%).

Table 3. Findings on Brain Computed Tomography or Magnetic Resonance Imaging Before Mitral Valve Operation

Finding	n (%)
Acute embolic infarct	44 (64)
Hemorrhage	3 (5)
Infarct + hemorrhage	14 (20)
Abscess + hemorrhage	2 (2)
Abscess + infarct	1 (2)
Infarct + hemorrhage + mycotic aneurysm	2 (2)
Mycotic aneurysm	1 (2)
Normal	2 (3)

infarction. This patient was a 67-year-old woman who presented with unilateral lower extremity weakness and severe MR and a large vegetation. Preoperative head CT scan showed an acute left cerebellar embolic stroke (4.3 cm \times 4.7 cm) with considerable mass effect within the posterior fossa. Postoperative CT scan reveled a new hemorrhagic transformation of the previous infarct in the left cerebellar hemisphere with extension into the fourth ventricle. In addition a new hemorrhagic focus in the right occipital lobe was observed. The patient was discharged with no new significant neurological changes compared with her preoperative exam.

Among the other 2 patients with new postoperative stroke that had experienced a preoperative stroke, 1 was a 35-year-old woman who presented with altered mental status and severe MR. Preoperative brain CT scan showed a large (4.3 cm \times 5.3 cm) hypodensity (ischemic infarct) within the right frontal lobe. MV replacement was performed. Postoperatively, the patient experienced a decline in mental status. Repeat CT scan showed a large (7 cm \times 4 cm) acute intraparenchymal hemorrhage on the left frontal lobe (the opposite side of the original stroke) with significant mass effect and midline shift. The patient died as a result of the stroke. The second patient was a 65-year-old man with aphasia and unsteady gait. Preoperative CT scan showed acute embolic infarct located in

the left cerebellar hemisphere (3.8 cm). Postoperatively, the patient developed altered mental status, right-sided neglect, and no fine motor skills on right side, as well as an expressive aphasia. CT scan findings included a new left posterior cerebral artery territory infarct and evolving preoperative infarct site with no evidence of hemorrhagic conversion. The patient was discharged to rehab after significant neurological improvement.

Kaplan-Meier survival analysis is shown in Figure 2. Estimated 5-year survival among patients with no preoperative stroke was 80% compared with 65% among patients with preoperative stroke (log-rank p=0.01).

Comment

The key findings of this study include (1) neurologic complication is common among patients presenting with MV IE and is frequently asymptomatic, (2) the presence of acute stroke is not associated with an increased risk of postoperative stroke in a setting with a programmatic emphasis on early surgical intervention, (3) hemorrhagic conversion of cerebral injury is exceptionally uncommon (1%) among patients with IE and acute stroke who undergo MV operation early after diagnosis of stroke, and (4) long-term survival is adversely affected by the presence of preoperative stroke.

Prevalence of Stroke in Active IE

Cerebrovascular injury is common in patients with MV IE [15]. Clinical stroke is observed in 20% to 30% of patients with left-sided IE [17]. In patients with active MV IE, 40% to 50% of patients have evidence of acute septic emboli on preoperative brain CT scan [18]. Embolic lesions can be identified in brain magnetic resonance imaging as many as 60% to 80% of patients with left-sided IE [19]. Asymptomatic brain lesions (silent stroke) has been reported in up to 30% of patients presenting with left-sided IE. Misfeld and colleagues [4] studied 1,571 patients with left-sided IE. 36% had isolated MV IE. Preoperatively, 25% had cerebral embolism confirmed by CT scan. Although the majority of patients presented with clinical

Table 4. Operative Characteristics

Variable	Overall $(N = 243)$	No Preoperative Stroke $(n = 174)$	With Preoperative Stroke $(n = 69)$	p Value
CPB time, minutes	138 ± 65	141 ± 68	131 ± 57	0.26
Cross-clamp time, minutes	112 ± 50	114 ± 52	107 ± 42	0.25
Operations				
MV				
Replacement	126 (52)	91 (52)	35 (51)	0.8
Repair	117 (48)	83 (48)	34 (49)	0.7
AV	74 (30)	59 (34)	15 (22)	0.06
TV	34 (14)	22 (13)	12 (17)	0.6
CABG	27 (12)	19 (11)	8 (11)	0.9

Values are mean \pm SD or n (%).

Table 5. Perioperative Outcomes

Variable	Overall ($N = 243$)	With No Stroke (n = 174)	With Stroke $(n = 69)$	p Value
New stroke	10 (4)	7 (4)	3 (4)	0.9
Bleeding requiring reoperation	19 (8)	14 (8)	5 (7)	0.47
Prolonged ventilation (>48 hours)	87 (36)	59 (34)	28 (40)	0.07
New dialysis	16 (7)	9 (5)	2 (3)	0.08
Time in ICU, hours	173 ± 322	170 ± 330	183 ± 302	0.7

Values are n (%) or mean \pm SD.

ICU = intensive care unit.

symptoms of stroke, one-third of patients were asymptomatic with only radiographic evidence of stroke. Vegetation size greater than 10 mm, positive blood culture, preoperative antibiotic therapy, and *S. aureus* bacteremia were found to be significant risk factors for cerebral embolism.

We routinely perform preoperative whole-body CT scan on all patients with MV IE not only to identify asymptomatic patients with stroke, but also to rule out secondary sources of infection. The rate of neurological complications in our study cohort was 28%, which is consistent with previously published studies. One-third of patients with radiographic evidence of stroke were asymptomatic. In our study postoperative neurologic outcomes among patients with preoperative stroke are not influenced by the presence or absence of preoperative neurologic symptoms.

Timing of Operation

Timing of MV operation in patients with active IE complicated with stroke is challenging. The traditional recommendation is that MV operation should be delayed for at least 4 weeks after the diagnosis of embolic stroke to allow time for restoration of the blood-brain barrier and healing of ischemic brain tissue [20]. This recommendation is based on a series of only 34 patients who were operated on an average of 3 weeks after the onset of stroke with stroke exacerbation in 2 (6%) patients [21].

There is strong accumulating evidence that early MV intervention for IE in the setting of acute stroke is safe and hemorrhagic conversion of an acute infarct is rare [22, 23]. Sorabella and colleagues [12] studied 308 patients who underwent surgery for active left-sided IE, 18% with preoperative stroke and 82% without preoperative stroke. The median time from diagnosis to surgery was 6 days. Only 38% had preoperative neuroimaging. Asymptomatic stroke was present in 22%. Operative mortality was 9.3% among patients with preoperative stroke and 7% among patients with no stroke (p = 0.57). Postoperative new stroke was observed in 5% and was not different between the 2 groups (9.4% with stroke versus 4.7% with no stroke; p = 0.19). The authors concluded that most patients with left-sided IE and neuroembolic event can safely undergo valve surgery in the early period after the diagnosis. One of the main limitations of their study is that more than 60% of the total cohort did not have preoperative neuroimaging and therefore it is possible that some patients who were categorized into the group with no preoperative stroke had in fact asymptomatic stroke.

Kang and colleagues [13] randomly assigned patients with left-sided IE, severe valve dysfunction, and large vegetations to early surgery (within 48 hours; 37 patients) or conventional treatment (39 patients). Thirty patients (77%) in the conventional-treatment group ultimately underwent surgery during the initial hospitalization or during follow-up. On admission, cerebral emboli were

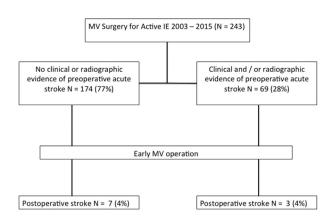


Fig 1. The rate of postoperative new stroke. (IE = infective endocarditis; $MV = mitral\ valve$.)

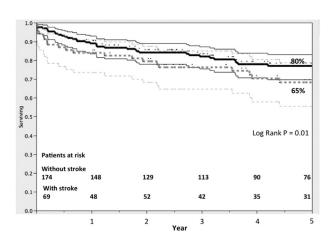


Fig 2. Kaplan-Meier 5-year survival among patients with (dashed line) or without (solid line) preoperative acute stroke.

identified in 30% among early surgery group and 28% among conventional group. In hospital death or embolic event at 6 weeks was 23% among conventional treatment group and 3% among early surgery group (p=0.01). New postoperative acute stroke occurred in 0% in the early surgery group and 13% in conventional group (p=0.005). The authors concluded that early surgery, as compared with conventional treatment, significantly reduced the composite end point of death from any cause or embolic events by effectively reducing the risk of systemic embolism among patients with IE.

In the current study, with a programmatic approach to operating early after the diagnosis of MV IE, the rate of new postoperative stroke was not different between with and without preoperative stroke. Given that only 1 (1%) patient had perioperative hemorrhagic conversion, we could not identify risk factors for conversion. The patient had a substantial preoperative infarct volume (4 cm). Given the low incidence of hemorrhagic conversion and the benefits of early operation, we do not delay MV intervention because of subarachnoid blood, cerebral infarction, or parenchymal hemorrhage that does not exceed 1.5 to 2 cm² in size.

Hemorrhagic Stroke

In this experience, 29% of neurologic injury associated with MV IE was intracerebral hemorrhage with or without ischemic stroke, which is consistent with other studies [24]. The size of the hemorrhage influenced the decision to proceed with the operation. We did not observe an increased risk of stroke among these patients with early operation. However, other studies have shown higher rate of mortality and neurologic complications after heart operations among patients with large intracranial blood volumes [25]. In a retrospective analysis, García-Cabrera and colleagues [25] studied 1,345 patients with left-sided IE treated medically or surgically; 25% experienced 1 or more neurological event during the IE episode. Ischemic stroke (56%) was the most common finding (small embolism = 72%; moderate-severe embolic complications defined as multiple cerebral embolisms or a single embolism affecting >30% of brain lobe =28%). Cerebral hemorrhage was found in 18%. Only 20% of 60 patients with cerebral hemorrhage underwent surgery and mortality was high among these patients. The percentage of new bleeds postoperatively was 50% in surgery within first 2 weeks, 33% in the third week, and 20% after 21 days of hemorrhagic stroke. In this study, 15 of 54 patients with moderate-severe ischemic brain lesions underwent surgery, 5 of them within 2 weeks (deaths = 2) and 10 after 2 weeks (deaths = 2). The authors concluded to delay surgery for left sided IE for 2 weeks for moderate-severe embolic stroke and 4 weeks for hemorrhagic stroke [25].

Limitations of this experience include the retrospective nature of the study. Only those patients who had postoperative neurologic symptoms underwent neuroimaging to identify new stroke. Some asymptomatic stroke patients might have been identified if all patients underwent cranial imaging after operation.

In conclusion, we found that MV surgery for patients with IE and acute stroke can be performed early with a low risk of postoperative neurologic complications. The likelihood of a postoperative stroke was not increased by the presence of a preoperative stroke. Hemorrhagic conversion of an infarct post-MV surgery is extremely rare. In most cases where indications for surgery are present, surgical intervention for MV IE complicated by acute stroke should not be delayed.

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DISCUSSION

DR VINAY BADHWAR (Morgantown, WV): Dr Ghoreishi, I would like to congratulate you on the elegance of your presentation. This is another example of how one can do clinical research and not only describe one's outcomes, but change how the rest of us practice. I need to recognize the leadership of Dr Gammie over the course of the last decade, who has focused on this one issue and helped us evolve from conservatism to active surgical therapy in endocarditis.

This issue is of particularly relevance now, since intravenous drug abuse is such a major issue throughout the United States; particularly in my area of Appalachia, where we encounter these cases almost on a daily basis. So this helps us refine our practice. I have 2 questions. First, in your manuscript and in your presentation, you outline that one of the tenants of why you would pursue an early approach is to try to intervene before there is structural degeneration of the valve, to facilitate earlier mitral repair. In your manuscript, you have 38 patients that had prosthetic valve endocarditis and 30% also that had aortic valve endocarditis, and your mitral repair rate was only about 48%. If you were to exclude those patients and focused on the isolated primary mitral patients, would you have information on the true repair rate for that subset of patients?

DR GHOREISHI: Thank you very much, Dr Badhwar, for your questions and also for accepting to review our paper.

Right now I have the data for those patients who had a history of prosthetic valve IE. I do not have the data on those patients

who had only isolated mitral. After excluding patients with a history of prior mitral valve repair or replacement, the repair rate was 55%.

DR BADHWAR: The second and last question is regarding your indications for operation being fungal culture, vegetation size and mobility, and persistent bacteremia. In your manuscript and in your presentation in the figure you showed that 71% of all patients were operated on within 7 days and 25% were operated on within 3 days. Now, I am not sure about the University of Maryland, but in most places it takes some time for the culture to persist. So would this suggest a philosophical change to your practice in that you are not actually following these guidelines of waiting for persistent bacteremia? Are we interpreting correctly that as soon as you have the diagnosis, stroke or no stroke, regardless of waiting for bacteremia, you would proceed with surgery?

DR GHOREISHI: The data that we have are the data of admission in our hospital to surgery, and usually when they get to us the results of their blood cultures are back. We excluded those patients who were chronic infective endocarditis. So I assume that all of these patients at least had a positive blood culture or culture negative overall. As long as the patient has the indication for operation, including severe MR or vegetation, we pursue with the operation. We do not wait for blood cultures to come back negative before going to the operating room.