Prosthetic Mitral Valve Thrombosis: Can Fluoroscopy Predict the Efficacy of Thrombolytic Treatment?

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Background—Thrombolysis (T) is an effective therapy for prosthetic valve thrombosis (PVT). Debate still exists as to which clinical or noninvasive finding best predict the result of T. The aim of the study was to investigate the role of fluoroscopy (F) to predict efficacy of T in pts with mitral PVT.

Methods—We evaluated 17 consecutive pts with bileaflet mitral PVT. F criteria for PVT were: abnormal disc motion and calculated opening angle >25°. T was carried out with tissue-type plasminogen activator (tPA; 100 mg over 3 hours followed by heparin infusion for 24 hours) and was considered successful when normalization of leaflet motion and opening angle occurred. Results were evaluated according to symptom duration (<21 days, early PVT; >21 days, late PVT) and to F pattern of PVT (blocked leaflet versus hypomobile leaflet).

Results—F showed disc motion alteration in 24 of 34 leaflets: 8 leaflets were blocked, whereas 16 were hypomobile. Early (12.7±6.1 days, range 3–21) and late (113±114 days, range 28–365) PVT was present in 8 and 7 pts, respectively. Thrombolysis was successful in 20 of 24 leaflets. Blocked leaflet fully recovered only in early PVT (n=4) pts, whereas they remained blocked in late PVT (n=4). On the contrary, in all of the cases with hypomobile leaflet, disc motion normalized regardless duration of symptoms and extent of disc motion reduction. Interestingly, 4 leaflets with late PVT was diagnosed as blocked by trans-thoracic (TTE). F showed a residual disc movement in all: they fully recovered after T. Two pts with late PVT had both leaflets affected (1 blocked +1 hypomobile); although blocked leaflet did not respond to T, the normalization of hypomobile significantly improved clinical condition.

Conclusions—F can predict result of T in mitral PVT. PVT with F evidence of hypomobile leaflet always recovers regardless of symptom duration and extent of disc motion reduction, suggesting that the small amount of thrombus needed to interfere with discs motion in bileaflet prostheses remains sensitive to T even after a long time. PVT with F evidence of blocked leaflet has a favorable response to T only in case of early PVT. Late PVT with blocked leaflet does not respond to T, suggesting a larger and stratified thrombus and the coexistence of pannus and, in our series, always required surgery. However, if a hypomobile leaflet coexists, T may be used to restore normal movement of hypomobile leaflet so that to improve patient clinical and hemodynamic condition before operation. (***Circulation***. 2003;108[suppl II]:II-79-II-84.)

Key Words: thrombolysis ■ prosthetic valve ■ thrombosis ■ fluoroscopy

P VT is a rare (0.2% to 6%/patient-year for left-sided prostheses) but potentially life-threatening complication of heart valve replacement.[1–3] Surgical intervention has been the traditional way to treat PVT. However, reported operative mortality may be as high as 69%, largely depending on patient functional class.[1,4] T has been reported to be an effective alternative treatment option.[4,5–11] However, the risk of cerebral embolism for left-sided PVT (5–10% for stroke with 6% death), major bleeding (5%), and recurrence PVT (11%) makes T still a debated issue. This controversy is fuelled by the lack of defined clinical and/or noninvasive variables that can predict T result so as to identify the ideal patient for this treatment. The aim of this study was to investigate the role of F, a quick, effective and readily available noninvasive method to study prosthesis dysfunction, to predict T effect in patients with PVT involving a bileaflet prostheses, ie, (the most used type of artificial heart valve) in mitral position (the site more at risk for thrombosis).

Methods

Seventeen consecutive patients (mean age 60±11 years; 13 women) were found to have mitral PVT according to F, TTE and trans-esophageal echocardiography (TEE) examinations. Patient characteristics at presentation are reported in Table 1.

Fluoroscopy was carried out through Siemens-Elema equipment (Siemens-Elema AB, Solna) with C-arm, as described previously.[12,13] The examination was considered successful when the "tilting disk" projection (with the x-ray beam parallel to both the valve ring plane and the tilting axis of the disk[s]) was obtained in order to calculate valve opening angle. Opening and closing angles were

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Patients' Characteristics at Presentation

Number of patients	17
Age (years)	60±11
Gender (Male/Female)	4/13
Type and size of bileaflet prosthesis	
CarboMedics	11 (⌀27=3, ⌀29=7, ⌀31=1)
Jyros	2 (⌀28=1, ⌀30=1)
St. Jude Medical	1 (⌀29=1)
Edwards-Duromedics	2 (⌀27=1, ⌀29=1)
Sorin Bicarbon	1 (⌀27=1)
Symptom duration (days)	66±92
<21 days (n=8 pts)	13±6
>21 days (n=9 pts)	113±117
Abnormal Fluoroscopy (n. of leaflets)	24/34
Blocked leaflet	8/24
Hypomobile leaflet	16/24
INR on admission	
>2.5	7/17 (41%)
≤2.5	10/17 (59%)
NYHA functional class	
II	11
III	3
IV	3
Heart rhythm (Sinus/atrial fibrillation)	8/9

defined as the distance between the 2 leaflets in the fully open and closed position (Figure 1). Fluoroscopic criteria for prosthetic valve obstruction were: persistent restriction of leaflet(s) motion with calculated opening angle greater than the mean value (+2SD) obtained in a reference group of patients with normally functioning valve of the same type.[12,13] Intra- and inter-observer variability for opening angle calculation has been reported previously.[12]

Two-dimensional and Doppler echocardiographic studies were performed using a Hewlett-Packard ultrasound unit (model Sonos 5500, M2424A); the system has 2.5 and 3.5 transducers (2-dimensional echocardiography), and 2.0, 2.5, and 1.9 MHz transducers for pulsed, continuous stearable, and stand-alone continuous Doppler, respectively. A complete 2-dimensional echocardiographic examination was performed to visualize the prosthesis in multiple cross-sectional views. Continuous wave mode was used to study flow across the prosthetic valves (apical view). Peak pressure

Figure 1. Fluoroscopy of a normally functioning CarboMedics bileaflet prosthesis in mitral position. A=opening angle. B=closing angle.

gradients were calculated from peak velocities according to the modified Bernoulli equation: $P=4.V2$; mean pressure gradients were obtained by planimetry with the software package of the ultrasound unit. Effective orifice mitral area was calculated with the pressure half-time method. Echocardiographic criteria for mitral prosthetic valve obstruction were: persistent restriction of prosthetic disc opening (M-mode) associated with mean Doppler pressure gradient higher than the mean value (+2SD) obtained in a reference group of 100 patients with normally functioning bileaflet mitral prostheses. Maximal and mean pressure gradients were $10.5±3$ and $4.1±2$ mmHg, respectively. Any mean pressure gradient value >8 mmHg was, therefore, considered as abnormal.[14]

TEE was performed with a 5 MHz or 5–6.2 MHz multiplane probes. Criteria for mitral PVT were: evidence of thrombus with or without altered mobility of the disk(s) and pathological regurgitation through the prosthesis. Thrombus was defined as a distinct mass of abnormal echoes attached to the prosthesis and clearly seen throughout the cardiac cycle.[15]

Study Protocol
The local ethical committee approved the study protocol, and written informed consent was obtained from each patient.

Oral anticoagulation was replaced by i.v. heparin for at least 48 hours before T. Each patient was than treated with 100 mg recombinant tPA as a 10-mg i.v. bolus followed by 90 additional mg over 3-hour continuous infusion. After T, i.v. heparin was reinstituted and titrated to obtain an ACT value of 180–200". After 24 hours, oral anticoagulation was started to achieve target (3.0–3.5) INR levels, whereas heparin was progressively discontinued.

Fluoroscopy and TTE were performed before T, at the end of infusion and 24 hours later. TEE was performed before and 24 hours after T. Therapy full success was defined as normalization of leaflet motion and opening angle by F associated with decrease of mean pressure gradient below 8 mmHg (if elevated at baseline) by TTE and dissolution of thrombus by TEE. Partial success was defined as either improvement of any leaflet motion and opening angle or normalization of leaflet motion and opening angle of 1 disk only in patients with PVT affecting both leaflets.

The effect of T, either success or failure, was evaluated according to the time interval from symptoms onset to detection of PVT (early PVT <21 days; late PVT >21 days) and to F finding (blocked leaflet versus hypomobile leaflet). The cut-off to differentiate early from late PVT was selected according to the "time-window" recommended for T in pulmonary embolism.[16]

Statistical Analysis
Data are presented as mean ± SD. Variations after T of mean pressure gradient and opening angle were evaluated with ANOVA analysis for repeated measurements. Post-hoc, post-treatment, and delayed measurements were compared by paired t-tests with the Bonferroni correction for multiple comparisons. Frequency of successes according to F findings (blocked versus hypomobile) was compared by Fisher's exact test. A $P<0.05$ were considered statistically significant.

Results
F detected abnormal disk motion in 24 of 34 leaflets (8 blocked and 16 hypomobile). TVP was defined as early (<21 days) in 8 patients and as late (>21 days) in 9 patients.

In-Hospital Results and Complications
Thrombolysis was full effective in 12 of 17 pts (70%). Partial success was detected in 2 of 17 (12%) and failure in 3 of 17 (18%). Overall, 5 of 17 (30%) pts required surgery. Per leaflet analysis showed full success in 19 of 24 (79%) and failure in 5 of 24 (21%) leaflets. There was no death. Major complications occurred in 2 pts (11.6%): 1 bleeding requiring transfusion and 1 coronary embolization. Minor complications
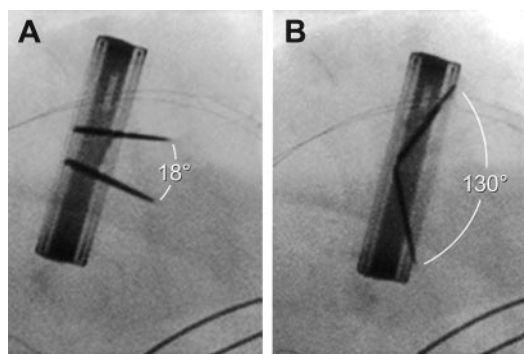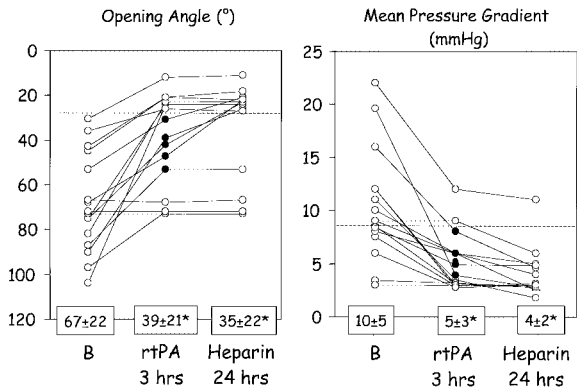
Figure 2. Individual changes in opening angle and mean pressure gradient following 3 hour infusion of tPA and 24-hour infusion of heparin. Dotted lines represent cut-offs (≤25° for opening angle and <8 mmHg for mean pressure gradient).
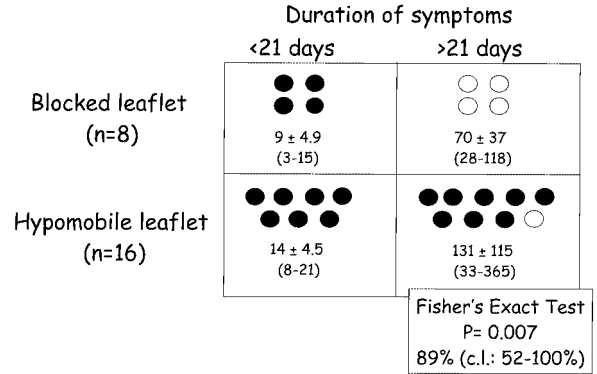

Figure 3. Effects of thrombolytic treatment according to duration of symptoms (< or >21 days) and type of leaflet motion abnormality by fluoroscopy blocked versus hypomobile leaflet). Each bullet represents one disk. Black bullets=full success. White bullets=failure.

occurred in 7 of 17 (41%) patients: 3 minor bleedings (gross hematuria in 1 and bleeding from the site of right heart catheterization in 2) and vague neurological complaints without objective neurological deficits in 4 cases.

Effects of T on Pressure Gradient and Opening Angle (Figure 2)

Mean pressure gradient at baseline was 10 ± 5 mmHg.[3–22] It decreased to 5 ± 3 mmHg ($P=.000$) soon after T and to 4 ± 2 mmHg ($P=0.000$ versus baseline, $P=NS$ versus end of T infusion) at 24 hours.

Six of 17 (35%) patients had normal pressure gradient at rest (5.3 ± 2.2 mmHg). It decreased to 3.3 ± 1.3 mmHg soon after T and to 3.2 ± 0.8 mmHg at 24-hour interval. The delta change at 24-hour interval was -2.2 ± 1.5 mmHg ($-31.5\pm21\%$).

All of the patients have an abnormal opening angle at presentation ($67\pm22°$, range: 30.5 to 104°). It decreased to $39\pm21°$ ($P=0.001$) and to $35\pm22°$ ($P=0.000$ versus baseline; $P=NS$ versus end of T infusion), after T and at 24 hours, respectively. Closing angles were similar and within normal limits in all of the patients at all steps ($132\pm9°$, $132\pm9°$, $132\pm10°$, $P=NS$).

Among the 11 patients having abnormal mean pressure gradient at rest (12.5 ± 4.7 mmHg), normalization after T occurred in 9. At this time, F showed an improved but still

abnormal opening angle in 5 of 9 (55%). This pattern resolved in 4 of 5 at 24 hours. The remaining patient did not additionally improve but refused an additional lytic treatment and was lost at F/U. There was no difference in mean pressure gradient at rest between patients who did or did not show abnormal F after T (12.6 ± 4.9 versus 10.9 ± 1.7 mmHg). However, percent δ change of mean pressure gradient was slightly lower in the former ($-49\pm19\%$) as compared with the latter ($-70\pm6\%$).

Effects of T According to Symptom Duration and F Findings (Figure 3)

T normalized leaflet motion in all of the cases (n=11) of early PVT regardless of whether they were hypomobile or blocked at baseline. In late PVT, on the contrary, all of the blocked leaflets (n=4) failed to reopen after T, whereas hypomobile leaflets (n=9) successfully reopened in 8 of 9. Figure 4 shows images of the patient with the longest (365 days) time interval from symptoms to PVT diagnosis who resolved after T. Four leaflets in late PVT patients were diagnosed as blocked by TTE. F showed a residual disc motion in all: they fully recovered after T. Two additional patients with late PVT and New York Heart Association (NYHA) functional class IV had both leaflet motion impaired (1 blocked +1 hypomobile leaflet) at presentation. Although blocked leaflet failed to respond to T, the normalization of the hypomobile disc
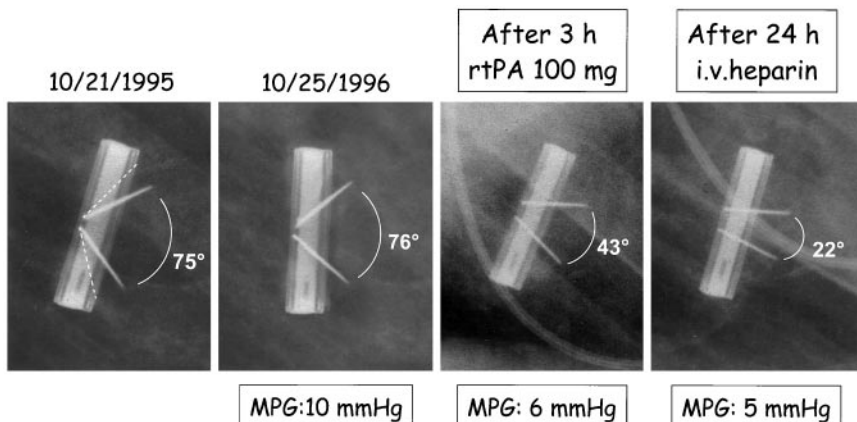

Figure 4. A case example of late PVT that favorably responded to therapy. Fluoroscopy shows an abnormal opening angle value at baseline (left) that remained stable at 1-year follow-up (mid-left). After tPA, opening angle improved but not normalized (mid-right). After 24 hours of heparin infusion, opening angle completely normalized. Mean pressure gradients for each phase are reported.

greatly improved patient clinical condition so that they were successfully reoperated on in a more stable hemodynamic situation.

There was a significant association ($P=0.007$) between hypomobile and success of T in late PV. Probability that a hypomobile leaflet recovered after T was 89% (confidence limits: 52–100%).

Discussion

This study highlights 2 important findings: (1) F is a useful noninvasive technique to detect PVT, to monitoring the effects and to predict the results of lytic treatment; and (2) T is a safe and effective treatment for left-sided PVT either as first choice of therapy or as a bridge to surgery.

Role of F and Doppler Echocardiography in Diagnosis of PVT

Noninvasive tests in diagnosis of PVT include F and TTE.[17–23] Since the introduction of TEE, ultrasound imaging has become the most used test in case of prosthesis dysfunction. This change happened without convincing scientific evidence of the superiority of 1 technique over the other. Moreover, it does not take into account that each method provides different kinds of information on prosthetic valve function and, therefore, should be considered as complementary (and not alternative) tests. We showed recently [14] that the concomitant use of F and TTE made a correct diagnosis of PVT in 85% of patients with suspected valve obstruction. Sensitivity, specificity, and positive predictive value were 87%, 78%, 80% and 75%, 64%, 57% for F and TTE, respectively. TEE was actually required to confirm diagnosis of PVT only in selected cases. Moreover, F has been found to be particularly indicated in bileaflet mitral PVT where Doppler mean pressure gradient has been reported to be normal in up to 33% of cases.[24] The present study confirms this observation showing 6 of 17 (35%) patients having normal Doppler study despite significant restriction in leaflet(s) motion at F (so called "Doppler silent PVT"). This occurrence may be explained by the peculiar design of bileaflet prostheses that, in case of block of only 1 disk, can maintain a near normal flow through the unimpeded leaflet so that to limit the hemodynamic impact of PVT. Patients with mitral PVT and single disk prostheses less frequently show this finding confirming the role of bileaflet design.[24] Thus, F should always be performed after a negative TTE especially in case of mitral bileaflet prosthesis. Once diagnosis of PVT is made by CF and TTE, TEE should be carried out to characterized thrombus type, size, and location so that to select the more appropriate treatment.

Role of F to Monitor Effects of T

T significantly reduced mean pressure gradient (while elevated at rest) and improved valve leaflet opening angle. Interestingly, 55% of patients whose pressure gradient normalized after T infusion still had concomitant abnormal leaflet motion at F, suggesting incomplete resolution of valve obstruction (so-called "pseudoresponders"). If lytic infusion is stopped at this time because of the normal pressure gradient (as suggested by the current guidelines)[25,26] the remaining

thrombus could be the trigger for a late rethrombotic process. If this holds true, some recurrences may be the result of an uncompleted resolution of the initial thrombotic process rather than the result of a new thrombosis. Thus, F should be carried out at regular interval during T to confirm Doppler changes. In case of partial result, if streptokinase or urokinase were used, infusion should be continued until normalization of leaflet motion or scheduled length of infusion. If tPA is administered, a stringent heparin infusion should be given for at least 24 hours and F repeated. If still abnormal, a second T course with a different agent should be considered. In our study, 4 of 5 pseudoresponders normalized F after 24-hour heparin treatment. Interestingly, despite the fact that there was no difference in mean pressure gradient at rest between patients who did or did not show concomitant leaflet motion normalization after T, the former group had a greater percent decrease ($-70\pm6\%$ versus $-49\pm18\%$) with all of the patients having a $>50\%$ value. This finding suggests that percent rather than absolute reduction in mean pressure gradient may be a sensitive parameter to indicate complete resolution of the thrombotic process. A larger number of cases is required to confirm this trend and to identify the best echocardiographic cut-off value.

Role of F to Predict T Effect

It is unknown whether the effect of T can be predicted by clinical or noninvasive variables. We evaluated the role of time interval from symptoms onset to PVT detection and the type of F abnormality. In early PVT (<21 days), all of the leaflets normalized following T regardless of the F pattern. This suggests that time delay before T in PVT is crucial. Although in previous studies the duration of symptoms did not appear to influence overall success rate, the majority of cases who favorably responded to T had symptoms duration <1 month.[4,5–9] In late PVT, on the contrary, we found a different response to T whether blocked or hypomobile leaflet was concerned. All blocked leaflet failed to respond to T, suggesting , as later confirmed at surgery, pannus formation as the cause of valve dysfunction. Actually, the detection of a normal motion of the other leaflet could be in favor of pannus rather than thrombosis. In fact, if thrombosis were the cause of valve dysfunction, since it is usually located at the valve hinge area in bileaflet prostheses,[3] it would have affected both leaflets motion. Thus, F evidence of single blocked disc in late PVT should raise the suspicion of pannus formation. Things are different for hypomobile leaflet. All but 1 reverted to normal after T. Reasons why long-standing PVT may be still responsive to T is unclear. It is likely that, because the amount of thrombus required to interfere with leaflet(s) motion in bileaflet prostheses may be minimal, this may more easily be dissolved by T even after a long time. Thus, distinction between blocked leaflet (BL) and hypomobile leaflet (HL) is vital. We think that F is the most accurate method for this purpose. We did not systematically compare F versus 2-dimensional echo in the assessment of leaflet motion. However, 2-dimensional echo successfully identified leaflet motion abnormality in $<60\%$ of cases. Moreover, patients with very initial or almost complete alteration of leaflet motion were those less likely to be identified by this
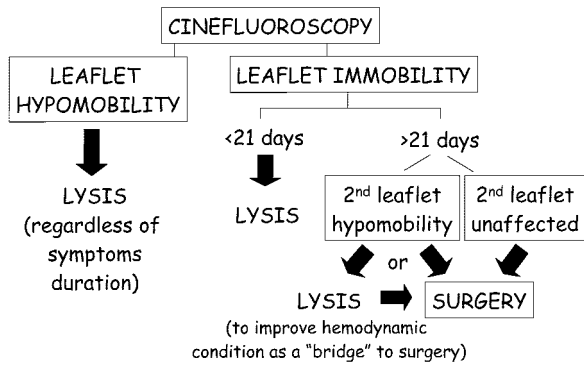
Figure 5. Flow chart showing treatment strategy for thrombosed mitral bileaflet prostheses (see text for details)

technique. Improvement in ultrasound technology would reduce this gap in the future.

Outcome of Lytic Treatment

The overall full and partial (combined) success and failure of T in our study was 70%, 12% (82%), and 18%, respectively. Rate of major complications was remarkably low (11.6%) with no mortality or stroke. These numbers compare favorably with previous studies dealing with similar patients-prostheses subset and definition of success.[4,5–11] The success/complication ratio of T in PVT is affected by several factors: patient selection, type of lytic regimen, time interval between onset of PVT and treatment, and site and type of prosthesis. The role of TEE in selecting patients and, hence, minimizing thromboembolic complications of T is an important although not yet established issue. Two recent studies reported a low embolic rate (0–5%) by excluding cases with left atrial or mobile thrombi.[5,10] It should also be noted that most episodes of embolism were transient and minor. Results of the present study should help to better define indications for T in PVT. So far, T has been accepted for critically ill patients in functional class III or IV in whom surgical intervention carries high risk or in patients with contraindications to surgery. In class I-II patients T cannot be recommended because of the low surgical mortality in this group as opposed to the embolic risk of 12–17% caused by T.[25] Data from our study, even if obtained in a small series of patients, suggest a systematic use of T regardless of NYHA functional class, especially in early PVT. In class III-IV patients with late PVT lysis may be the first-line treatment even in patients amenable to surgery, provided that a favorable F pattern is present (2 hypomobile leaflets or 1 blocked and 1 hypomobile leaflets). The improvement of leaflet(s) motion by T allows these patients to be reoperated in a more stable hemodynamic condition in order to reduce mortality.

Clinical Implications

Figure 5 outlines our present protocol for managing patients with suspected PVT of mitral bileaflet prostheses. Initial diagnosis is made by combined F and TTE. The key to diagnosis is leaflet motion restriction rather than increased pressure gradient. Differentiation between blocked and hypomobile leaflet is then made by F. Patients with hypomobile leaflet and without contraindications should receive T regard-

less duration of symptoms. Patients with blocked leaflet, on the contrary, should be treated with T only in case of early PVT. If symptoms duration is >21 days patients should be referred to surgery. If concomitant hypomobile leaflet coexists that leads to severe hemodynamic impairment, one should consider T for this disc normalization so as to stabilize both hemodynamic and clinical condition as a bridge to surgery.

Limitation of the Study

The study number of patients was small and focused only to mitral bileaflet PVT. We do not known if results can be extrapolated to aortic bileaflet prostheses or to single disk prostheses. The cut-off (21 days) to differentiate early from late PVT was selected according to the "time-window" recommended for T in pulmonary embolism.[16] However, symptoms in PVT may be nonspecific or sometime lacking at all, making a separation between groups difficult if not impossible. Each patient received only 1 course of T. It is possible that repeated T treatment would have improved overall rate of success.[5,8] However, our institutional policy is to give a second or third T course only in patients who showed partial result after first treatment.

Conclusions

In patients with thrombosed mitral bileaflet prostheses, F allows for the identification of patients with "Doppler silent" PVT, to identify pseuroresponders so as to guide duration of lytic treatment and to predict effect of T. Therefore, F should be always part of the diagnostic work-up of suspected PVT. TTE should be performed in selected cases for diagnosis or more widely to assess the risk of embolization and to determine the aggressiveness of therapy.[5,27]

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