Original Article

Effect of thrombolytic therapy on the patterns of post myocardial infarction ventricular septal rupture

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ABSTRACT

Objectives: Ventricular septal rupture (VSR) is a rare but feared complication after myocardial infarction (MI). The objective of this study was to investigate the effects of thrombolytic therapy on the patterns of VSR following MI.

Methods: 30 consecutive patients admitted to a single tertiary level cardiac hospital with a diagnosis of acute MI and developed VSR in the hospital were included. The effect on thrombolytic therapy on the formation of VSR and its clinical outcome was studied.

Results: Out of 30 patients, 15 patients received thrombolytic therapy.10 received early (<12 h) and 5 received late (>12 h). The median time to post MI VSR formation was significantly shorter in thrombolysis group compared to non thrombolysis group at 1 vs 3 days($p = 0.026$). The median time for VSR formation was shorter in early thrombolysis group compared to late thrombolysis group at 1 vs 3 days ($p = 0.022$). There was no difference between late and no thrombolytic therapy (3 vs 3 days, $p = 0.672$). There was no significant difference in the mortality between thrombolytic and no thrombolytic therapy ($p = 0.690$). Patients treated medically had a significant higher mortality compared to patients treated surgically ($p = 0.005$).

Conclusion: Thrombolytic therapy results in an earlier presentation of VSR after MI. This earlier presentation may be due to reduction in the number of patients developing late VSR after thrombolytic therapy, while the number of patients developing an early VSR remaining unaffected. Despite improvements in medical therapy and percutaneous and surgical techniques, mortality with this complication remains extremely high.

1. Introduction

Ventricular septal rupture (VSR) is a rare but often fatal complication of acute myocardial infarction (MI). In prethrombolytic era the reported incidence of post MI VSR was 1%–2%.[1,2] However introduction of reperfusion therapy like thrombolysis and primary percutaneous intervention (PCI) has significantly reduced its incidence with only 0.2% reported in the GUSTO I trial[3]. Several factors have been identified to be associated with an increased risk of developing a post MI VSR like female sex, hypertension, anterior MI, prior angina, and increasing age.[3,4] In the prethrombolytic era, outcomes after the development of VSR were extremely poor, with an in-hospital mortality of 45% in surgically treated patients and 90% in those managed medically.[1,2,5–7] Factors predicting increased mortality include cardiogenic shock, longer duration of bypass, previous infarct, right heart compromise, inferior myocardial infarction and size of infarct.[3,4,8–15]

In prethrombolytic era it was reported that VSR typically occurs within the first week of MI with a mean time from symptom onset of 3–5days.[1,8,9] In thrombolytic era studies have given conflicting evidence regarding the time of onset of VSR after MI. In GUSTO-1 trial the mean time of development of VSR after thrombolysis was 1 day.[3] However in the SHOCK trial there was no difference in the time of development of VSR between the thrombolytic and non thrombolytic groups.[16]

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The aim of the present study was to evaluate the difference in the time of onset of VSR after MI between thrombolytic and non-thrombolytic patients admitted to a single tertiary care cardiac hospital. Furthermore we sought to study the factors associated with the increased mortality in patients who develop VSR.

2. Methods

In this prospective study done between January 2012 to December 2012, 30 patients with diagnosis of post MI VSR were included. Enrolment criteria included patients presenting with chest pain lasting ≥ 20 min and satisfying the World Health Organization criteria of acute MI and developing VSR within the hospital. Exclusion criteria included patients who had developed VSR outside the hospital and referred for further management. Informed consent was taken from all patients. Ethical clearance was taken before conducting the study.

The time of onset of chest pain was considered as the time of onset of the acute myocardial infarction. Acute myocardial infarction was diagnosed using the standard 12 lead electrocardiogram and cardiac enzyme (World Health Organization criteria). The time from onset of myocardial infarction to thrombolysis was separated into early (<12 h) or late (>12 h); this was the time from initial onset of pain to the time when the patient received thrombolysis. The time of onset of the VSR was assumed to coincide with the abrupt onset of symptoms and new murmur as documented in the patient's clinical record. The diagnosis of VSR was confirmed with Trans thoracic echocardiography in all cases. Patients were divided into two groups- thrombolytic group and non-thrombolytic group. The thrombolytic group was further divided into patients receiving thrombolysis within 12 h and those receiving thrombolysis 12 h or later. Streptokinase was used as thrombolytic agent in all the patients. All patients were analyzed for risk factors, demographics, clinical profile, treatment and prognosis.

Table 1
Baseline clinical characteristics.

Variable	Total (n = 30)	Thrombolysis group (n = 15)	Non Thrombolysis group (n = 15)
Age in years (Mean ± SD)	63.4 ± 9.8	66.07 ± 6.1	60.73 ± 12.1
Sex (Male)	18 (60%)	10 (66.66%)	8 (53.3%)
Risk factors			
Diabetes	15(50%)	8(53.3%)	7(46.6%)
Hypertension	12(40%)	7(46.6%)	8(53.3%)
Dyslipidemia	5(33.33%)	3(20%)	2(13.33%)
Smoking	10(33.33%)	5(33.33%)	5(33.33%)
History of angina	4(13.33%)	1(6.6%)	3(20%)
Family history	4(13.33%)	3(20%)	1(6.6%)
Old MI	3(10%)	1(6.6%)	2(13.33%)
Presentation			
AWMI	18(60%)	8(53.33%)	10(66.66%)
IWMI	12(40%)	7(46.66%)	5(33.33%)
Ejection fraction (Mean ± SD)	44.07± 6.4	45.87 ± 7.1	42.27 ± 5.1
CK-MB (Mean ± SD)	121.5± 139.84	82.47 ± 76.4	160.53 ± 177.1
Treatment			
Heparin	27(90%)	13(86.66%)	14(93.33%)
Aspirin	30(100%)	15(100%)	15(100%)
Clopidogrel	29(96.66%)	15(100%)	14(93.33%)
Beta blocker	14 (46.66%)	8(53.33%)	6(40%)
ACE Inhibitor	15 (50%)	9(60%)	6(40%)
Diuretics	15(50%)	7(46.66%)	8(53.33%)
Inotropes	26(86.66%)	13(86.66%)	13(86.66%)
NTG	3(10%)	1(6.6%)	2(13.33%)
Examination			
Pulse >100	19(63.33%)	9(60%)	10(66.66%)
Systolic BP < 90	19(63.33%)	11(73.33%)	8(53.33%)
Raised JVP	22(73.33%)	10(66.66%)	12(80%)
Killip I	13(43.33%)	9(60%)	4(26.66%)
Killip II	10(33.33%)	3(20%)	7(46.66%)
Killip III	2(6.66%)	1(6.66%)	1(6.66%)
Killip IV	5 (16.66%)	2 (13.33%)	3 (20%)
Urea (mg/dl) [Mean ± SD]	58.40 ± 49.59	61.67 ± 52.79	55.13 ± 47.81
Creatinine(mg/dl) [Mean ± SD]	1.35 ± 0.72	1.24 ± 0.51	1.45 ± 0.89
IABP	19(63.33%)	11(73.33%)	8(53.33%)
Total occlusion of infarct artery	21(70%)	9(60%)	12 (80%)
30 days mortality	16 (53.33%)	8(53.33%)	8(53.33%)
1 year mortality	21(70%)	11(73.33%)	10(60%)

MI: Myocardial infarction; AWMI: Anterior wall myocardial infarction; IWMI: Inferior wall myocardial infarction; NTG: Nitroglycerin; JVP: Jugular venous pulse; IABP: Intra aortic balloon pump.

Mean follow up was 1 year and 100% complete. It was at regular intervals with clinical visits or telephone interviews.

3. Statistical analysis

All statistical analysis was performed using SPSS statistical software (version 16.0, SPSS Inc., Chicago, Illinois). Categorical variables are expressed as counts and percentage. Continuous variables are expressed as mean ± SD or median ± interquartile range (25th percentile to 75th percentile) as appropriate. Categorical variables, expressed as percentages, were analyzed with chi-square or Fisher's exact test. Continuous variables were analyzed using two-tailed t-test or Mann–Whitney U test. Univariate factors with p value ≤ 0.25 were analyzed using binary logistic regression analysis. A two tailed p-value less than 0.05 was used to indicate statistical significance.

4. Results

There were 30 eligible patients with the diagnosis of post MI VSR who had developed the complication in the hospital. The baseline clinical demographics of these patients are presented in Table 1. There was no significant difference between the two groups with respect to risk factors, clinical profile or treatment except for the time of VSR formation which was significantly less in thrombolysis group. Out of total 30 patients, 12(40%) of them were female, the mean (SD) age was 63.4 (9.8) years, 18 (60%) of them presented with anterior wall MI, 4 (13.3%) of them had a history of angina, and 12 (40%) of them had hypertension. All of these factors were previously found to be significantly associated with VSR. 18 had apical VSR and 12 has basal VSR. Size of the VSR varied from 4 mm to 16 mm with average of 8 mm in diameter. 3 (10%) of them had old MI, 20 (66.6%) of them had pulse >100 beats/minute, 19 (63.3%) of them had blood pressure (BP) ≤ 90 mm Hg and 12(40%) had inferior wall MI; all these were previously found to be associated with increased mortality. 7 of them had biventricular failure. In this study, pulse >100 beats/min and BP ≤ 90 mm Hg were found to be associated with increased mortality in univariate analysis. However multivariate analysis showed that it was not statistically significant. There was no statistically significant difference in the mortality between thrombolysis and no

thrombolysis group (p = 0.690). Even though it was not statistically significant mortality tended to be higher in patients with biventricular failure. Mortality data of the patients are summarised in Table 2.

Regarding effect of thrombolysis on development of VSR, 15 (50%) patients received thrombolytic therapy. 10 of them received early (<12 h after MI) and 5 of them received late (>12 h) thrombolytic therapy. The other 15 were not given thrombolysis due to late presentation. The data for time to VSR formation is detailed for each group in Table 3. The median time for development of VSR in patients with thrombolytic therapy was significantly shorter than in patients without thrombolytic therapy (1 vs. 3 days, p = 0.026). Significant difference was also found between patients who were thrombolysed early (median = 1 day, range 1-4 days) compared to patients with late thrombolysis (median = 3 days, range 2–4 days p = 0.022). There was no statistically significant difference in the development of VSR between late (median = 3 days, range 2-4 days) and no thrombolysis group (median = 3 days, range 1-8 days, p = 0.672). Table 4 illustrates the effect of thrombolysis on the time of development of VSR.

Angiographically 21 (70%) patients had total occlusion of infarct related artery (13 Left anterior descending artery (LAD), 7 Right coronary artery and 1 left circumflex artery). Out of 18 LAD arteries 11 were wraparound arteries. 14 (46%) had single vessel, 10 had double vessel (33.3%) and 6 (20%) had triple vessel disease. 15 (50%) patients underwent surgical intervention. 14 (93.3%) of them underwent both coronary artery bypass surgery (CABG) and VSR repair, and the remaining 1 (6.6%) patient underwent VSR repair alone. Timing of the surgery was decided by the surgeon and mainly based on the clinical condition of the patient. The median day of surgery from the onset of VSR was 3 days (Range 1-42 days). There were 2 (13.3%) peri-operative deaths. Mortality at 30 days was 20% (n = 3) and at 1 year 46.66% (n = 7). 15 patients were treated medically. Patients treated medically were significantly older and had advanced heart failure compared to those treated surgically. The 30 days mortality in this group of patients was 86.66% (n = 13) and at 1 year it was as 93.3% (n = 14). There was a significant difference in mortality between medically treated and surgically treated patients, with very high mortality in the former group (p = 0.005). Intra aortic balloon pumps (IABP) was inserted in 19(63.3%) patients. Surgical data is summarised in

Table 2

Analysis of risk factors effect on mortality.

Risk factor	Number	Number (%) of deaths	Univariate analysis P value	Multivaraite analysis P value (CI)
Pulse				
<100/min	10	4 (40%)	0.011	0.082 (0.78-56.28)
>100/min	20	17(85%)		
Systolic BP				
>90 mm Hg	11	4(36.36%)	0.011	0.082 (0.78-56.28)
≤ 90 mm Hg	19	17(89.47%)		
Raised JVP				
< 3 cm	21	16(76.19%)	0.283	–
> 3 cm	09	05(55.55%)		
Location of MI				
AWMI	18	12(66.66%)	0.689	–
IWMI	12	9 (75%)		
Thrombolysis				
Yes	15	11 (73.33%)	0.756	–
No	15	10 (60%)		

BP-Blood pressure; JVP-Jugular venous pressure; MI- myocardial infarction; AWMI- Anterior wall MI; IWMI-Inferior wall MI

Table 3
Patients numbers in terms of days from myocardial infarction to VSR and thrombolytic therapy

Number of days from MI to VSR	No thrombolysis (n = 15)	Early thrombolysis (n = 10)	Late thrombolysis (n = 5)	Total
1	1	9	0	10
2	2	0	1	3
3	7	1	3	11
4	1	0	1	2
5	0	0	0	0
6	2	0	0	2
7	1	0	0	1
8	1	0	0	1
	Total = 15	Total = 10	Total = 5	Total = 30

Table 4
Influence of Thrombolysis on time to VSR formation.

Median time to VSR formation(days) Median ± SD (range)	Thrombolysis (n = 15) 1.00 ± 1.08 (1–4)	No Thrombolysis (n = 15) 3.00 ± 2.0 (1–8)	P value 0.003
Median time to VSR formation(days) Median ± SD (range)	Early Thrombolysis (n = 10) 1.00 ± 0.63 (1–3)	Late Thrombolysis (n = 5) 3.00 ± 0.7 (2–4)	P value 0.003
Median time to VSR formation(days) Median ± SD (range)	Late Thrombolysis (n = 5) 3.00 ± 0.7 (2–4)	No Thrombolysis (n = 15) 3.00 ± 2.0 (1–8)	P value 0.672

Table 5
Surgical data: Number (%).

Treatment	
Surgical	15 (50%)
Medical	15 (50%)
Surgical details	
VSR repair alone	1(6.6%)
VSR repair + CABG	14 (93.33%)
IABP used	19(63.33%)
Immediate post op death	2 (13.33%)

VSR-ventricular septal rupture; CABG-Coronary artery bypass grafting; IABP-Intra-aortic balloon pump.

Table 6
Influence of Surgery on Mortality.

Mortality	Surgery (n = 15)	Medical (n = 15)	P value
Mortality at 30 days	3(20%)	13(86.66%)	<0.001
Mortality at 1 year	7(46.66%)	14(93.33%)	0.005

Table 5. The influence of treatment on mortality is summarised in Table 6.

5. Discussion

VSR remains an infrequent but often fatal complication of acute myocardial infarction. The use of thrombolytic agents have reduced the incidence from 1%-2%[1,2] in the prethromobolytic era to 0.2%[3] in the thrombolytic era. In the prethrombolytic era VSR occurred most often in the first week of AMI, typically three to five days after onset of symptoms.[1,8,9] Few studies with the use of thrombolytic agents have shown that the time of formation of VSR has reduced to 1 day.[3,17] In GUSTO I trial the mean time from infarction to development of VSR was found to be 1 day.[3] Becker and colleagues also reported similar findings.[10,13] Rhydwen et al. showed that the median time for VSR formation was 1 day in thrombolytic patients compared to 5.5 days in patient without thrombolysis.[17] They also showed that patients treated with early thrombolysis (<12 h) developed VSR early compared to patients

with late thrombolysis (>12 h). However in SHOCK trial there was no difference in the time of development of VSR between the thrombolytic and non thrombolytic groups.[16] In the present study we show that time to VSR formation in acute MI after thrombolytic therapy is significantly shorter. We also show that late thrombolytic therapy does not appear to have this effect. This raises the possibility that only early thrombolytic therapy accelerates the time from MI to VSR. Similar to Rhydwen et al. we used 12 h from the onset of pain to thrombolytic therapy as cut off between early and late groups. However all patients received thrombolysis within 8 h of the onset of symptoms. The median time to VSR formation in patients without thrombolysis was 3 days similar to studies quoted from prethrombolytic era.

Several mechanisms have been proposed for acceleration of post MI VSR formation in thrombolytic patients. Thrombolytic therapy appears to reduce the overall incidence of cardiac rupture,[3,4] probably by restoring vessel patency, salvaging myocardium, and preventing on going infarct expansion resulting in a decreased incidence of late myocardial rupture.[3,8,18–20] The GUSTO investigators analysis of mortality within one day of thrombolytic therapy, however, shows that deaths within four hours of treatment were not influenced by the establishment of arterial patency, that patients were more likely to have severe cardiac dysfunction and larger infarcts.[21] Patients, who develop a post myocardial infarction VSR, although unlikely to die this early, are also more likely to have an occluded artery and larger infarct.[3,8,15,20,22,23] Thus it is likely that in patients who develop an early post Myocardial infarction VSR thrombolytic therapy is unlikely to salvage already necrosed myocardium and have little influence on the incidence or time of development of early VSRs. Overall therefore there is probably a reduction in the number of patients developing a late VSR while there is retention, or slight increase in the number of patients developing an early VSR. This would move the median and mean time of post-myocardial infarction VSR earlier, giving an apparent acceleration of events.

Another mechanism proposed is that reperfusion following thrombolysis may potentially promote haemorrhage and dissection in the myocardium, thus accelerating the risk of rupture.[24] Rupture was also seen within one to two days in the smaller group of patients treated with primary angioplasty.[24] Reperfusion injury

has been shown to increase infarct size in animal models, which could increase the incidence and decrease the time to post-myocardial infarction cardiac rupture.[25–27] Against this are the findings that the majority of post-myocardial ruptures occur when the infarct related artery is occluded.[3,8,15,20,22,23] The GUSTO investigators also provided no evidence that arterial patency leads to reperfusion injury in terms of cardiac rupture or left ventricular dysfunction.[21] Finally, thrombolytic agents increase the circulating and infarct levels of plasmin, a proteolytic enzyme capable of degrading collagen,[28] independently of vessel patency, probably resulting in increased proteolytic activity at the infarct site. This could reduce collagen locally, which is implicated in infarct expansion.[29] This again could accelerate the time to and increase the incidence of post-MI VSRs. The exact role of this mechanism on the timing of post MI VSR formation is unclear.

Thrombolytic therapy increases the incidence of haemorrhagic infarct independently of vessel patency with the haemorrhagic area almost exclusively confined to the infarct area and not associated with infarct expansion.[30–32] Although thrombolytic therapy increases the number of infarcts with haemorrhage, the incidence of myocardial rupture, is probably not significantly affected as nearly all myocardial ruptures occur in the small percentage of infarcts that have extensive haemorrhage in any case. It is therefore unlikely that post MI VSR is a haemorrhagic complication of thrombolytic therapy. Indeed cardiac rupture events are not increased in patients receiving concurrent anti-coagulants along with thrombolytic therapy.[4] Our study also supports this, as late thrombolytic therapy appeared to have no influence on the time from myocardial infarction to VSR. It would still seem reasonable, however, to hypothesise that the fibrinolytic state induced by thrombolytic therapy could accelerate and slightly increase the possibility of rupture in large haemorrhagic infarcts. The required number of cases to demonstrate this, however, would probably need to be larger than reported to date. Our angiographic data, consistent with previous studies, show that patients who develop VSRs after acute MI are more likely to have total occlusion of the infarct artery.[3] This suggests that the pathophysiology of acute VSR involves sudden, severe ischemia, leading to extensive myocardial necrosis, and that patients who do not reperfuse with thrombolysis are at increased risk of mechanical complications. This group of patients also had more extensive coronary disease and poor LV function.

VSR is associated with extremely high mortality even in thrombolytic era despite improvements in medical therapy and percutaneous and surgical techniques[3]. In our study overall 30 days mortality was 53.5% and 1 year mortality was 70%. This suggests that if the patient survives the initial admission, the long term prognosis is relatively good. Previous studies suggested that patients with old MI, inferior infarct, pulse >100/min and BP <90 mm Hg are associated with high mortality.[3,4,8–15] The reasons proposed for worse outcome with inferior infarct is that, it is associated with complex VSRs and located in the inferobasal portion of the septum and therefore were more difficult to approach surgically.[8] Anterior infarcts were more commonly associated with simple, through-and-through defects in the apical septum, which tend to be more easily repaired. Our study did not show any difference in mortality, probably due to improvement in surgical techniques over the years. However patients with tachycardia and hypotension had trend towards high mortality suggesting extensive myocardial damage and poor LV function associated with this group of patients. Thrombolysis was not associated with increased mortality contrary to some studies which suggested that it may increase the mortality in patients with VSR.[4,17]

6. Study limitations

This was a single center nonrandomized study, so it has its inherent limitations. The number of patients involved even though comparable to other studies, is still relatively small with limited statistical power. The incidence of VSR was not calculated because patients who developed VSR outside the hospital and referred for further management were not included in the study. Only Trans thoracic echocardiography was used for diagnosis of VSR. Trans oesophageal echocardiography was not used as the diagnosis was clear in transthoracic images and most of these patients were sick. Pulmonary capillary wedge pressure was not checked in any of the patients. Streptokinase was the only thrombolytic agent used in all patients. We do not know the effect of other thrombolytic agents on the development of VSR. Finally trans catheter closure of VSR was not attempted in any of the patients. We do not know the effect of this procedure on mortality of these high risk patients.

7. Conclusions

Thrombolytic therapy is known to decrease the incidence of VSR following acute myocardial infarction. However it results in an earlier presentation of VSR compared to patients without thrombolytic therapy. The acceleration in the VSR formation after thrombolytic therapy would not appear to be a reperfusion injury or haemorrhagic complication. There is a reduction in the number of patients developing a late post MI VSR after thrombolytic therapy, while the number of patients developing an early post MI VSR remains the same or is not reduced to the same degree. This moves the mean and median time from MI to VSR earlier and this is the most likely mechanism for the apparent acceleration of events leading to post MI VSR formation in patients treated with thrombolytic therapy. Thus this earlier presentation appears to be due to be the positive impact of thrombolytic therapy in reducing the incidence of late post-MI VSRs. Most of these patients have totally occluded culprit arteries. Outcome in these patients remains extremely poor, with a mortality rate of 46% in patients undergoing surgical repair and 93% in those treated medically. More effective ways to predict, prevent, and treat this devastating complication are needed.

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