ORIGINAL ARTICLE

Influence of thrombolytic therapy on the patterns of ventricular septal rupture after acute myocardial infarction

G R Rhydwen, S Charman, P M Schofield

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See end of article for authors' affiliations

Correspondence to: Dr G R Rhydwen, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; c.rhydwen@ntlworld.com

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Background: Post-myocardial infarction ventricular septal defect (VSD) complicates ~2% of myocardial infarctions. Thrombolytic therapy may accelerate the time from myocardial infarction to VSD formation. The effects of thrombolytic therapy in patients with a post-myocardial infarction VSD were investigated.

Method: Demographic, procedural, and event data were retrospectively analysed in patients transferred to a regional cardiothoracic centre with the diagnosis of post-myocardial infarction VSD over five years.

Results: Twenty nine patients were analysed; 15 received thrombolytic therapy: 10 (<12 hours) early and five (≥12 hours) late. The median time to post-myocardial infarction VSD was shorter with thrombolytic therapy at 1 *v* 5.5 days (p=0.01). The median time to post-myocardial infarction VSD was shorter with early compared with late thrombolytic therapy at 1 *v* 6 days (p<0.01). There was no difference between late and no thrombolytic therapy, 5.5 *v* 6 days. Patients treated with thrombolytic therapy had a trend towards higher mortality at 11/15 (73%) compared with 5/14 (36%) (p=0.066). Twenty five (86%) patients had surgery. All four not having surgery died. Surgical survival was 13/25 (52%) at discharge and six months of follow up. Within the surgical group survival with prior thrombolytic therapy was 4/25 (25%) and 9/13 (69%) without (p=0.07).

Conclusion: There appears to be an earlier presentation of post-myocardial infarction VSD when thrombolytic therapy has been used. An early presentation can carry a worse prognosis and may have implications for the identification and treatment of this life threatening complication.

Cardiac rupture is responsible for 10%–15% of all in-hospital deaths after myocardial infarction. Mortality after myocardial infarction has been proved to have fallen with thrombolytic therapy.[1–6] The incidence of myocardial rupture leading to ventricular septal defect (VSD) has also declined with thrombolytic therapy with an incidence of only 0.2% reported in the GUSTO-I trial.[7–10] The mortality after VSD formation, however, has changed little over the last 30 years. If medically treated the mortality is approximately 90%–100% falling to ~50% if there is surgical intervention.[7 8 11–15] Several factors have been identified to be associated with an increased risk of developing a post-myocardial infarction VSD (female, hypertension, anterior myocardial infarction, thrombolytic therapy, prior angina, and increasing age),[7 8 15] or an increased mortality after a VSD has formed (signs of shock, longer duration of by-pass, previous infarct, right heart compromise, inferior myocardial infarction, size of infarct).[7 8 12–19]

VSD complicating an acute myocardial infarction is traditionally reported as complicating ~1%–2% of acute myocardial infarctions.[11 12] In the prethrombolytic era it was classically reported that VSD formation after infarction typically occurred within the first week at a median time from 2–5 days with 30%–40% occurring in the first 48 hours.[11 12 14 18 19] More recently it has been reported that thrombolytic therapy may reduce the time from myocardial infarction to VSD.[7 15]

We therefore assessed the influence of thrombolytic therapy on the time to presentation of post-myocardial infarction VSD in patients transferred to Papworth hospital (a cardiothoracic tertiary referral hospital) with the diagnosis of post-myocardial infarction VSD.

METHODS

We retrospectively analysed the demographic, procedural, and event data from the clinical records of all patients transferred to Papworth Hospital with the diagnosis of post-myocardial infarct ventricular septal rupture from 1995 to December 1999. All the patients were referred from district general hospitals. The diagnosis of VSD had to be confirmed with an echocardiogram at surgery or at necropsy. Patients diagnosed as having a post-infarct VSD who were not referred, or died before transfer, were not included.

The time of onset of chest pain was considered as the time of onset of the acute myocardial infarction. The time from onset of myocardial infarction to thrombolysis was separated into early (<12 hours) or late (≥12 hours); this was the time from initial history of onset of pain in the patient records to the time when the patient received thrombolysis. Acute myocardial infarction was diagnosed using the standard 12 lead electrocardiogram and cardiac enzyme (World Health Organisation criteria).[20] The time of onset of the VSD was assumed to coincide with the abrupt onset of symptoms and new murmur as documented in the patient's clinical record. Of the 33 patients referred, the time from myocardial infarction to VSD formation could only be analysed in 29 of the patients. The time from myocardial infarction to VSD formation could not be accurately assessed in the remaining four patients, as two had two myocardial infarctions in the week before the diagnosis of VSD, and the other two had no hospital admission during their myocardial infarction, making accurate timing impossible. The remaining patients were separated into patients receiving thrombolysis compared with those not receiving thrombolysis. The thrombolysis group was further divided into patients receiving thrombolysis within 12 hours and those receiving thrombolysis 12 hours or later.

Table 1 Patient baseline demographics; results are number (%) unless otherwise stated

	Total (n=29)	Thrombolysis (n=15)	No thrombolysis (n=14)
Mean (SD) age (years)	68 (7.6)	69 (6.6)	67.5 (8.6)
Male	21 (72)	12 (80)	9 (64)
Myocardial infarction			
Anterior	14 (48)	8 (53)	6 (43)
Inferior	15 (15)	7 (47)	8 (57)
Previous myocardial infarction	5 (17)	3 (20)	2 (14)
Risk factor			
Smoker	7 (24)	2 (14)	5 (33)
Diabetic	6 (21)	4 (27)	2 (14)
Hyperlipidaemia	7 (24)	3 (20)	4 (29)
Hypertension	12 (41)	5 (33)	7 (50)
Family history	11 (35)	7 (47)	4 (29)
Previous angina	2 (7)	2 (13)	0
Examination			
Blood pressure ⩽90 mm Hg	13 (45)	7 (47)	6 (43)
Pulse >100 beats/min	18 (62)	8 (53)	10 (71)
Raised JVP	16 (55)	6 (40)	10 (71)
Medication			
β-Blocker	4 (14)	4 (14)	0
Calcium blocker	6 (21)	3 (20)	3 (21)
Ace inhibitor	8 (28)	2 (13)	6 (43)
Diuretic	13 (45)	5 (33)	8 (57)
Aspirin	25 (86)	13 (86)	12 (86)
Nitrate	4 (14)	2 (14)	2 (13)
Inotropes	29 (100)	15 (100)	14 (100)
Statin	3 (10)	1 (7)	2 (14)
Heparin	4 (14)	1 (7)	3 (21)

There were no significant differences for any of the variables.
JVP, jugular vein pulse.

Table 2 Analysis of risk factors' effect on mortality

Risk factor	No	No (%) deaths	p Value
Pulse (beats/min)			
<100	10	4 (40)	0.27
⩾100	19	12 (63)	
Raised			
JVP >2 cm	16	8 (50)	0.71
JVP normal	13	8 (62)	
Blood pressure (systolic) (mm Hg)			
⩽90	13	9 (69)	0.26
>90	16	7 (44)	
Location of myocardial infarction			
Anterior	14	7 (50)	0.71
Inferior	15	9 (60)	
Thrombolysis			
Yes	15	11 (73)	0.066
No	14	5 (36)	

JVP, jugular vein pulse.

Statistics

Each categorical factor is described as the number and the percentage of patients with that characteristic. Results are summarised with mean (SD) or median (interquartile range) as appropriate. Risk factors for death post-VSD formation were analysed using Fisher's exact test. Comparisons between thrombolysis groups were made using the Mann-Whitney test.

RESULTS

There were 29 eligible patients referred with the diagnosis of ventricular septal rupture after acute myocardial infarction. Eight (30%) were female, the mean (SD) age was 68 (7.6) years, 14 (48%) had an anterior infarction, two (7%) had a history of prior angina, and 12 (41%) had hypertension; these were all found previously to be risk factors for cardiac rupture.[7 8 15] Five (17%) patients had a previous myocardial infarction, 19 (66%) had a presenting pulse rate ⩾100 beats/min, 15 (52%) had an inferior infarct, and 13 (45%) had a systolic blood pressure ⩽ 90 mm Hg; these were all found previously to be associated with increased mortality.[7 8 12–19] A full summary of the patient demographics can be found in table 1. None of the above risk factors were significantly associated with mortality. Patients treated with thrombolytic therapy, however, had a trend towards a higher mortality by hospital discharge; 11/15 (73%) died compared with 5/14 (36%) of the patients not treated with thrombolytic therapy (p=0.066). Becker and colleagues found a similar trend in patients receiving early thrombolytic therapy compared with placebo.[16] The mortality data is summarised in table 2.

In the analysis of the influence of thrombolytic therapy on the time to VSD formation, 15 (52%) patients received thrombolytic therapy, (10 early at <12 hours and five late at ⩾12 hours from onset of myocardial infarction), and 14 (48%) patients received no thrombolytic therapy. The reason for not receiving thrombolytic therapy in all the cases was due to late presentation by the patient. The data for time to VSD from myocardial infarction is detailed for each group in table 3 and fig 1.The median time from myocardial infarction to VSD in the thrombolytic therapy group was significantly shorter than the group that received no thrombolytic therapy at 1 day *v* 5.5 days (p=0.01). The median time from myocardial infarction to ventricular septal rupture was also significantly shorter in patients who received early thrombolytic therapy (<12 hours, 10 patients) compared with patients who received late thrombolytic therapy (⩾12 hours, five patients) at 1 day *v* 6 days (p<0.01). There was no significant difference between patients receiving late thrombolytic therapy and the patients who received no thrombolytic therapy, 5.5 days *v* 6 days (p=0.6). See table 4 and fig 2.

Twenty five (86%) of the patients had surgical intervention, 17(68%) had a repair and coronary artery by-pass combined procedure, and eight (32%) had a repair alone. The median time from the diagnosis of VSD to surgery was 1 day, range (1–82) with 17 (68%) having surgery on the day of admission and 21 (84%) having surgery within one week of VSD formation. There

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

No of days from myocardial infarction to VSD	No not having thrombolysis	Thrombolysis			Total
		No	Early	Late	
1	0	9	9	0	9
2	1	0	0	0	1
3	1	0	0	0	1
4	3	1	0	1	4
5	2	2	1	1	4
6	3	1	0	1	4
7	3	2	0	2	5
8	0	0	0	0	0
9	0	0	0	0	0
10	1	0	0	0	1
Total No of patients	14	15	10	5	29

Table 4 Influence of thrombolysis on time to VSD formation

	Thrombolysis (n=15)	No thrombolysis (n=14)	p Value
Median time to VSD formation (days)	1	5.5	0.01
	Early thrombolysis (n=10)	Late thrombolysis (n=5)	
Median time to VSD formation (days)	1	6	0.001
	Late thrombolysis (n=5)	No thrombolysis (n=14)	
Median time to VSD formation (days)	6	5.5	0.62

Table 5 Surgical data; results are number (%) unless otherwise stated

Treatment	
Surgical	25 (86)
Medical	4 (14)
Surgical procedure details	
By-pass time (SD)	95 (27.5) min
Time from referral to surgery	Median 1 day (range 1–55)
VSD repair alone	8 (32)
VSD repair +CABG	17 (68)
IABP inserted	21 (84)
Death on table	3 (12)
Survival to discharge	13 (52)
Survival at 6 months	13 (52)

CABG, coronary artery by-pass grafting; IABP, intra-aortic balloon pump.

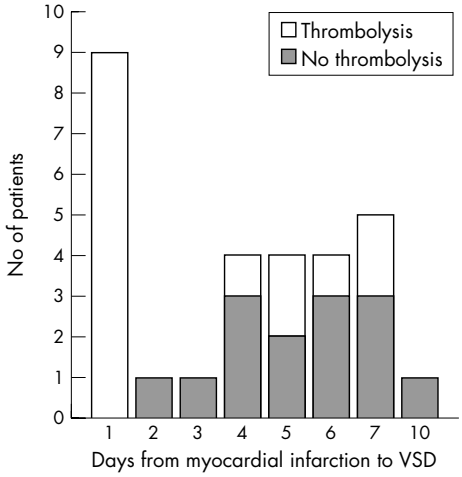

Figure 1 Time from myocardial infarction to VSD for patients receiving or not receiving thrombolysis.

was one perioperative stroke and two perioperative deaths. The mean (SD) by-pass time was 97 (21) min. All four patients not having surgery died, two arrested before the procedure could be carried out, and two were felt to be too unwell to be operative candidates; both died shortly after admission. Twenty one (84%) had preoperative intra-aortic balloon pumps inserted and all were treated with intravenous inotropes. Treatment with thrombolytic therapy in the surgical patients, however, again showed a trend towards a worse mortality at 8/12 (75%) of those treated dying compared with 4/13 (30%) of those not treated (p=0.07). Overall 13 (52%) patients survived to hospital discharge and all 13 survived to six month follow up. A summary of the surgical data can be found in table 5.

DISCUSSION

The time to VSD formation after myocardial infarction is possibly accelerated by thrombolytic therapy compared with the quoted time frame in the prethrombolytic era.[7 15 16] We show that the time to VSD formation after acute myocardial infarction in patients receiving thrombolytic therapy is significantly shorter. Despite small numbers, we also report that late thrombolytic therapy doesn't appear to have this effect. This raises the possibility that only early thrombolytic therapy accelerates the time from myocardial infarction to VSD. We used 12 hours from the onset of pain to thrombolytic therapy as the cut off between the early and late groups. However all the patients receiving early thrombolysis actually received therapy within six hours of the onset of symptoms.

The median time to post-myocardial infarction VSD in our non-thrombolytic therapy group is longer than in the

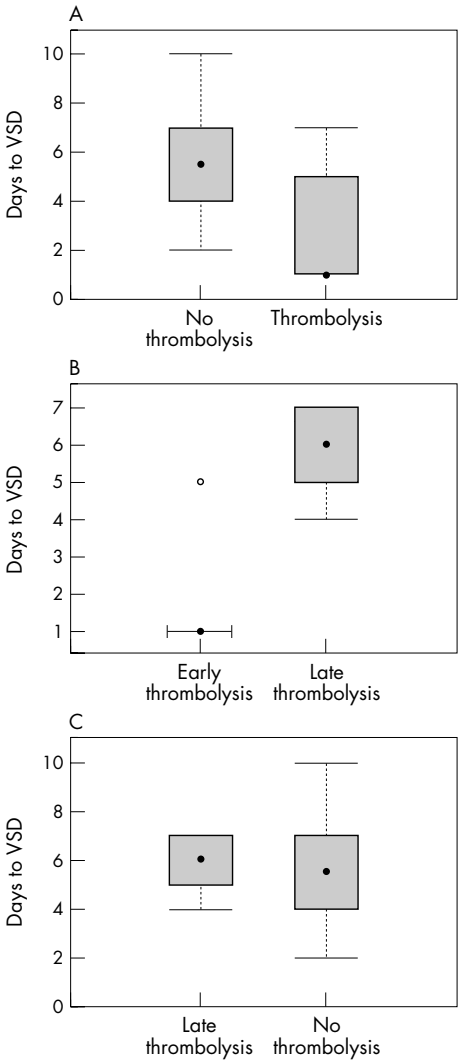

Figure 2 Box whisker plots of time to VSD from myocardial infarction with respect to thrombolysis.

prethrombolytic era at 5.5 compared to the 2–5 days classically quoted, with only one in the first 48 hours compared with the 20%–40% in the prethrombolytic period.[11 12 19 21–23] Our study was not an necropsy survey thus excluding patients dying before presentation. Patients considered too unwell for further intervention while at the district general hospital, were also excluded. Further patients who presented to hospital within 24 hours, with an infarct predestined to form an early VSD, are more likely to have received thrombolytic therapy, thus preselecting themselves into the thrombolytic group. All these factors potentially reduce the number of patients with early VSDs seen in our non-thrombolytic therapy group.

There are several possible mechanisms for the acceleration of post-myocardial infarction VSD formation after thrombolytic therapy. The median time to cardiac rupture is variable ranging from 2–5 days in the prethrombolytic era, with 25%–40% occurring within 48 hours of the myocardial infarction.[11 12 19 21–23] Thrombolytic therapy appears to reduce the overall incidence of cardiac rupture,[7 15] probably by restoring vessel patency, salvaging myocardium, and preventing ongoing infarct expansion resulting in a decreased incidence of late myocardial rupture.[1 4 7 11 19 21] 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.[24] Patients who develop a post-myocardial infarction VSD, although unlikely to die this early, are also more likely to have an occluded artery, larger infarct, and more extensive coronary disease.[7 18 19 21 25 26] Thus in patients who develop an early post-myocardial infarction VSD thrombolytic therapy is unlikely to salvage already necrosed myocardium and have little influence on the incidence or time of development of early post-myocardial infarction VSDs. Overall therefore there is probably a reduction in the number of patients developing a late VSD while there is retention, or slight increase in the number of patients developing an early VSD. This would move the median and mean time of post-myocardial infarction VSD earlier, giving an apparent acceleration of events.

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.[27–29] Against this are the findings that the majority of post-myocardial ruptures occur when the infarct related artery is occluded.[7 18 19 21 25 26] The GUSTO investigators also provide no evidence that arterial patency leads to reperfusion injury in terms of cardiac rupture or left ventricular dysfunction.[24] Thrombolytic agents increase the circulating and infarct levels of plasmin, a proteolytic enzyme capable of degrading collagen,[30] 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.[31] This again could accelerate the time to and increase the incidence of post-myocardial infarction myocardial VSDs. The exact role of this mechanism on the timing of post-myocardial infarction VSD formation is unclear.

Necropsy evaluation of post-infarct ventricular rupture shows three distinct variations: a direct slit like rupture, a ragged tear rupture, and a haemorrhagic rupture.[11 19] In the prethrombolytic era the majority of infarcts are classified as being non-haemorrhagic, with haemorrhagic infarcts considered rare.[32 33] In infarcts leading to rupture however, ~90% are classified as having moderate or severe haemorrhage at the infarct site, although only 9% were thought to be a haemorrhagic rupture, and ~12% as a combination of haemorrhage and myocardial tear.[21] 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.[34–36] 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-myocardial infarction VSD is a haemorrhagic complication of thrombolytic therapy. Indeed cardiac rupture events are not increased in patients receiving concurrent anticoagulant therapy as with other haemorrhagic complications of thrombolytic therapy.[15] Our study also supports this, as late thrombolytic therapy appeared to have no influence on the time from myocardial infarction to VSD. 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. There was a trend to increased mortality in patients treated with thrombolytic therapy who went on to develop a post-myocardial infarction VSD. Becker and colleagues found a similar relationship for cardiac rupture in patients receiving early thrombolytic therapy from data in the LATE trial.[16] However when looking at patients from the United States National Registry of Myocardial Infarction, they found although cardiac rupture was more prevalent in patients treated with thrombolytic therapy, overall these patients still had a lower comparative in-hospital mortality.[8] In

our study the median time to surgery in patients receiving thrombolytic therapy was shorter at five compared with seven days. It has been reported that early surgery, and early VSD formation after myocardial infarction are associated with increased mortality.[13 17 37] This may explain the trend to increased mortality we found, although our trial was not designed to address mortality data.

CONCLUSION

Thrombolytic therapy appears to result in an earlier presentation of ventricular septal rupture after acute myocardial infarction. Thrombolytic therapy is known to reduce the overall incidence and in hospital mortality of this life threatening complication.[7 8 12] Earlier presentation of a VSD, usually within the first 24 hours, is possibly associated with a worse prognosis irrespective of thrombolytic therapy because if a VSD occurs early the myocardial infarction is more likely to be larger and haemorrhagic than if the VSD occurs late.[21]

The acceleration, in post-myocardial infarction VSD formation after thrombolytic therapy would not appear to be a haemorrhagic complication, or reperfusion injury. The role of increased collagen breakdown due to increased plasmin levels is unclear. There is a reduction in the number of patients developing a late post-myocardial infarction VSD after thrombolytic therapy, while the number of patients developing an early post-myocardial infarction VSD remains the same or is not reduced to the same degree. This moves the mean and median time from myocardial infarction to VSD earlier, and this is the most likely mechanism for the apparent acceleration of events leading to a VSD post-myocardial infarction treated with thrombolytic therapy. Thus this apparent acceleration of events appears to be due to be the positive impact of thrombolytic therapy in reducing the incidence of late post-myocardial infarction VSDs. This mechanism requires further investigation, although the low incidence of this complication makes this difficult.

Authors' affiliations

G R Rhydwen, S Charman, P M Schofield, Cardiology Unit, Papworth Hospital, Cambridge, UK

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