Thrombosis & Haemostasis: Research

Open Access

Austin Publishing Group

Special Article - Trauma

Streptokinase-Inducing Hypotension in Acute Myocardial Infarction but Blood Pressure Normalizing in Acute Massive Pulmonary Embolism; Why?

Elsayed YMS*
Critical Care Unit, Fraskour Central Hospital, Egypt

***Corresponding author:** Yasser Mohammed Hassanain Elsayed, Critical Care Unit, Fraskour Central Hospital, Damietta Health Affairs, Egyptian Ministry of Health (MOH), Damietta, Egypt

Received: April 24, 2020; **Accepted:** May 25, 2020; **Published:** June 01, 2020

Abstract

Streptokinase is a well-known hypotension inducing agent in acute myocardial infarction. Hypotension is more frequently in inferior myocardial infarction especially if associated with right ventricular dysfunction. On the opposite side, acute massive pulmonary embolism is accompanied by obstructive shock and hypotension. Administration of streptokinase in massive pulmonary embolism dramatically normalizing the blood pressure rather than improving the clinical condition. So, the suggesting hypothesis: streptokinase-inducing hypotension in acute myocardial infarction but blood pressure normalizing in acute massive pulmonary embolism. The research objectives to evaluate this hypothesis might include: Why is streptokinase-inducing hypotension in acute myocardial infarction but normalizing the blood pressure in acute massive pulmonary embolism? The author concluded that streptokinase-inducing hypotension in acute myocardial infarction but blood pressure normalizing in acute massive pulmonary embolism is still obscure.

Keywords: Streptokinase; Hypotension; Acute myocardial infarction; Massive pulmonary embolism; Normalizing the blood pressure

Abbreviations

AMI: Acute Myocardial Infarction; BP: Blood Pressure; C: Complement; PE: Pulmonary Embolism; PESI: Pulmonary Embolism Severity Index Scoring; Plgn: Plasminogen; Pm: Plasmin; RVD: Right Ventricular Dysfunction; SBP: Systolic Blood Pressure; SK: Streptokinase; STEMI: ST-Elevation Myocardial Infarction

Introduction

Streptokinase

Scoping and relevant serial history: Streptokinase (SK) is a thrombolytic medication and enzyme [1]. The drug was listed in the World Health Organization's (WHO) List of Essential Medicines (EML) as the safest and most effective medicines needed in a health system [2]. Through several years of investigations, Tillett WS. with his student Sherry S, et al. were initially discovered SK in 1933 from beta-hemolytic streptococci species [1,3]. Indeed, Tillett accidentally noticed that streptococci agglutinated in test tubes that contained human plasma but not in those that contained human serum [3]. This was the key step. The prime candidate for this agglutinating activity was fibrinogen. On the other hand, Tillett hypothesized that fibrinogen is adsorbed on the surface of streptococci indicating that the plasma free of fibrinogen. He found that any plasma containing streptococci would not clot, due to lack of free fibrinogen (a key clotting factor) [3]., Garner et al. (27 June 1933) [4] concluded that the presence of fibrinolytic activity of hemolytic streptococci. Sherry S et al. had confirmed using SK as a thrombolytic drug in the management of Acute Myocardial Infarction (AMI) [1]. However, treatment of fibrinous pleural exudates, hemothorax, and tuberculous meningitis was another serendipitous uses [5]. Sherry et al. with his colleges (1958) started using SK in cases of AMI. However, early trials that used SK infusion produced inconsistent results. Indeed, Rentrop et al. and his colleagues (1979) had initiated the intracoronary SK infusion with reperfusion rates that ranging from 70% to 90% in ST-Elevation Myocardial Infarction (STEMI) [5]. Lastly, Gruppo Italiano per la Sperimentazione Della Streptochinasi nell'Infarto Miocardico (GISSI) trial (1986) offered validated SK as an established, effective, and fixed therapy for its use in AMI [1].

Mechanism of action and biological value

Streptokinase is one of the most famous fibrinolytics [6]. Streptokinase composes complexes with human plasminogen can hydrolytically stimulate other unbound plasminogen (Plgn) by activating via bond cleavage to yield Plasmin (Pm). However, three domains to SK, symbolized α (residues 1–150), β (residues 151–287), and γ (residues 288–414). Each domain independently binds Plgn [6]. Plasmin would lyse fibrin that is the main component of blood thrombi, thereby dissolving clots. Extra-synthesis of Pm caused by SK breaking down clots. The ordinary stimulation of Plgn is by proteolysis of the Arg561—Val562 bond [7]. The amino group of Val562 constitutes a salt-bridge with Asp740, which motivates a modulation alteration producing the active protease Pm. When SK is present, it binds to Plgn to form the SK-Plgn complex that converts the substrate Plgn to Pm. Residues 1–59 of SK regulate its capacity to induce an active site inbound Pg by non-proteolytic pathogenesis and to activate substrate Pg in a fibrin-independent manner. Thereafter, complex reposition into an active complex although the Arg561–Val562 bond stays intact. Thus, another residue must replace for the free amino group of Val562 and supply an antagonist for Asp740 in this active complex [8]. Two candidates for this antagonist have been

Citation: Elsayed YMS. Streptokinase-Inducing Hypotension in Acute Myocardial Infarction but Blood Pressure Normalizing in Acute Massive Pulmonary Embolism; Why?. Thromb Haemost Res. 2020; 4(3): 1046.

suggested: Ile1 of SK and Lys698 of Plgn. The deletion of Ile1 of SK significantly inhibits its capacity to induce an active site in Plgn, which backups the hypothesis that stabilization of a salt bridge between Ile1 of SK and Asp740 of Plgn is essential for SK to induce an active site in Plgn by a non-proteolytic mechanism [9]. In contrast with the Ile1 substitutions, the Lys698 mutations also diminished the dissociation constant of the SK complex by 15 to 50 fold. These observations suggest that Lys698 is involved in the genesis of the initial SK-Plgn complex [10]. Streptokinase is naturally created by *Streptococci* spp. bacteria, which use this enzyme to break up blood clots so that they can spread from the initial site of infection. It can also stimulate fibrin [11]. It is similar, in both function and chemistry, but, staphylokinase (Sak) present in *Staphylococcus aureus*. Staphylokinase is an essential virulence factor [12]. Both enzymes are included in phages [13]. Streptokinase can be used to prevent postoperative adhesions, especially abdominal surgery such as appendectomy, gall stones, and hysterectomy [14].

Streptokinase and hypotension

Determinants of post-SK hypotensive response in STEMI: Hypotension is a common side effect of SK [15]. The most important determinant of hypotension in STEMI patients receiving SK is the rate of drug infusion. However, there is a scarceness of data on the other factors associated with SK-related hypotension [16].

Mechanism of hypotension in STEMI is treated with streptokinase: The possibility of post-SK hypotensive response may be due to a decrease in Peripheral Vascular Resistance (PVR), reflecting a lowering in plasma viscosity caused by the reduction in plasma fibrinogen, a major component of plasma viscosity [18]. This hypothesis was rejected by Gemmil et al. (1993) [15]. They found no association between the fall in fibrinogen, corrected plasma viscosity, and Blood Pressure (BP) response. They also rejected the hypothesis that Fibrin Degradation Products (FDPs) can activate the prostaglandin-prostacyclin system causing vasodilatation and hypotension, as they found no relationship between BP and the fibrin product D-dimer, or changes in fibrinogen [18]. The BP changes post-treatment with SK drug AMI are common but well-tolerated [15]. The mechanism of hypotension is still uncertain but is not related to past-exposure to streptococcal antigen [15]. Whether Complement (C) activation is the cause of transient hypotension during SK infusion in patients with STEMI. The mechanism of hypotension observed post the infusion of SK is not via C-activation, and thus how SK induces hypotension is still unknown?. However, it is a curious finding that some patients develop substantial complement activation and some none at all [17]. Because SK is produced from streptococcal bacteria, it often causes febrile reactions and other allergic problems. It can also cause hypotension that appears to be dose-related [19].

Hypotension in STEMI patients receiving streptokinase has poor prognostic value: It is concluded that although patients with low Systolic Blood Pressure (SBP) during SK infusion have high mortality. So, the level of SBP before the infusion is more mightily accompanied by the outcome [20]. Hypotension is not dependant on pretreatment SK resistance titer, anti-SK IgG concentration, changes in plasma fibrinogen, B-β 15–42 peptide, and D-dimer [15].

Acute massive pulmonary embolism

Scoping and risk stratification classification: Pulmonary Embolism (PE) is a frequent cardiovascular disease and approximately 60-112/100,000 individuals [21]. It is considered the third most common cause of cardiovascular mortality. It is responsible for 100,000-180,000 deaths/year [22,23]. However, PE is usually classified as massive (high-risk), submassive (intermediate-risk), and non-massive (low-risk). It is an initial essential step to evaluate the demanded treatment. Risk stratification scores are also used to assess both morbidity and mortality [24]. Massive PE is defined as suspected or confirmed PE in the presence of shock, sustained hypotension, the absence of a pulse, or persistent profound bradycardia [21,24,25]. In high-risk (massive) PE: there are shock or hypotension (SBP <90 mmHg or decrease in SBP of ≥40 mmHg from baseline) and echocardiographic Right Ventricular Dysfunction (RVD). These patients are about <5% of acute PE patients [26]. The early hospital mortality rate in massive PE patients is ranged between 25% to 65% [27]. Submassive PE is defined as suspected or confirmed PE with RVD in the absence of shock [21,24,25]. Intermediate-risk (submassive) PE: Patients without shock or hypotension but with signs of RVD (non-massive) PE: Patients without shock/hypotension and no signs of RVD or with PESI scoring <1. The early mortality rate in both submassive non-massive PE is below 1% [28].

Table 1: Pulmonary Embolism Severity Index (PESI) scoring system.

Variable	Points
Age	Age in years
Altered mental status (AMS)	60
Cancer	30
Systolic blood pressure (SBP)< 100 mm Hg	30
Pulse rate ≥ 100 beats per minute	20
Respiratory rate (RR) > 30 breaths per minute	20
Temperature < 36° C	20
Arterial oxygen saturation (O2 sat.) < 90%	20
Male gender	10
Chronic heart failure (CHF)	10
Chronic pulmonary disease	10
PESI Class	**Score**
Class I (very low 30-day mortality risk)	≤ 65 points
Class II (low mortality risk)	66–85 points
Class III (moderate mortality risk)	86–105 points
Class IV (high mortality risk)	106–125 points
Class V (very high mortality risk)	> 125 points

Modified from Aujesky D, et al. (2005) and Dundar Y, et al. (2013)

Thrombolytics guidelines and pulmonary embolism: Indeed, acute PE patients in the absence of shock, hypotension, or signs of RVD are considered to have a low 30-day mortality risk [29]. It should be noted that both the European guidelines (grade 1B) (2014) [25] and the CHEST guidelines (class III, level B) (2016) [30] recommend against the administration of thrombolytics in patients with acute PE in the absence of hypotension. So, thrombolysis with streptokinase is not recommended for these patients [25]. A PESI class of I or II (Table 1) should immediate clinicians to think in outpatient treatment [29,31]. Hemodynamically unstable PE patients are the target for either intravenous thrombolytics or surgical thrombectomy [32].

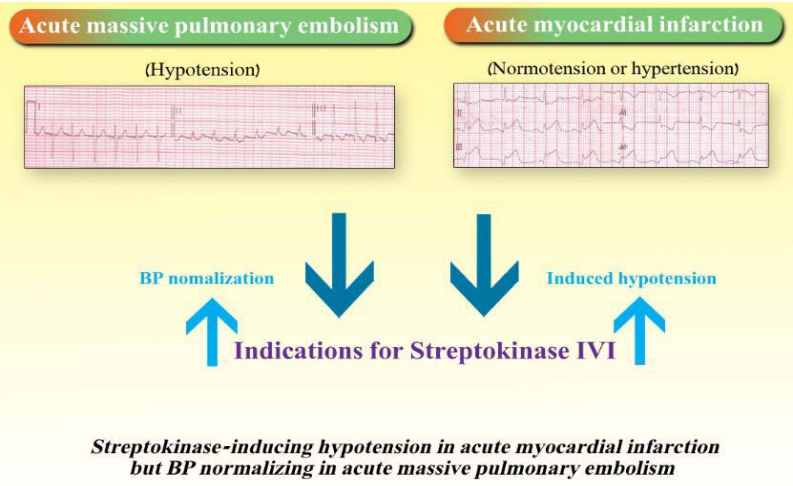

Figure 1: Blood pressure configuration post-streptokinase in myocardial infarction and pulmonary embolism.

Thrombolytic medications are acting by transform native Plgn to Pm, which in turn breaks down the fibrin of thromboemboli, causing clot lysis [32]. Streptokinase, urokinase, and alteplase are the only indicated agents for the acute massive PE with hypotension [33-37].

Hypotension is an important parameter in the pulmonary embolism severity index (PESI) scoring

The result: Administered streptokinase according to the standard protocol improved markedly the hemodynamic status, and blood pressure normalized [38].

Discussion and Conclusion

• The research objectives to evaluate this hypothesis might include: Why is streptokinase-inducing hypotension in acute myocardial infarction but normalizing the blood pressure in acute massive pulmonary embolism? (Figure 1).

• Despite there are many suggested an explained hypotheses for interpretation for streptokinase-inducing hypotension in acute myocardial infarction such as;

1. Decrease in Peripheral Vascular Resistance (PVR), reflecting a lowering in plasma viscosity caused by the reduction in plasma fibrinogen, a major component of plasma viscosity.

2. An association between the fall in fibrinogen, corrected plasma viscosity, and Blood Pressure (BP) response.

3. The hypothesis that Fibrin Degradation Products (FDP s) can activate the prostaglandin-prostacyclin system causing vasodilatation and hypotension.

4. Complement (C) activation.

5. Past-exposure to the streptococcal antigen.

But all these hypotheses were rejected.

•, On the other hand, regards the normalizing the blood pressure in acute massive pulmonary embolism, unfortunately, the clinical cardiovascular and pulmonary literature entirely did not support this result.

• So, The author concluded that streptokinase-inducing hypotension in acute myocardial infarction but blood pressure normalizing in acute massive pulmonary embolism is still obscure and unclear.

• The author recommended widening the research on this subject.

Acknowledgment

I wish to thank Dr. Ameer Mekkawy; M.sc. for technical support.

References

1. Sikri N, Bardia A. A history of streptokinase use in acute myocardial infarction. Tex Heart Inst J. 2007; 34: 318–327.
2. World Health Organization. World Health Organization model list of essential medicines: 21st list 2019.
3. Sherry S. Personal reflections on the development of thrombolytic therapy and its application to acute coronary thrombosis. Am Heart J. 1981; 102: 1134-1138.
4. Tillett WS, Garner RL. The fibrinolytic activity of hemolytic streptococci. J Exp Med 1933; 58: 485–502.
5. Cathie IA. Streptomycin-streptokinase treatment of tuberculous meningitis. Lancet. 1949; 1: 441.
6. Mundada LV, Prorok M, DeFord ME, Figuera M, Castellino FJ, Fay WP. Structure-function analysis of the streptokinase amino terminus (residues 1-59). J Biol Chem. 2003; 278: 24421–24427.
7. Young KC, Shi GY, Wu DH, Chang LC, Chang BI, Ou CP, et al. Plasminogen activation by streptokinase via a unique mechanism. J Biol Chem. 1998; 273: 3110–3116.
8. Loy JA, Lin X, Schenone M, Castellino FJ, Zhang XC, Tang J. Domain interactions between streptokinase and human plasminogen. Biochemistry. 2001; 40: 14686–14695.
9. Wang S, Reed GL, Hedstrom L. Deletion of Ile1 changes the mechanism of streptokinase: evidence for the molecular sexuality hypothesis. Biochemistry. 1999; 38: 5232–5240.
10. Wang X, Lin X, Loy JA, Tang J, Zhang XC. Crystal structure of the catalytic domain of human plasmin complexed with streptokinase. Science. 1998; 281: 1662–1665.
11. Wang H, Lottenberg R, Boyle MD. Analysis of the interaction of group A streptococci with fibrinogen, streptokinase and plasminogen. Microbial Pathogenesis. 1995; 8: 153–166.

12. Bokarewa MI, Jin T, Tarkowski A. Staphylococcus aureus: Staphylokinase. The International Journal of Biochemistry & Cell Biology. 2006; 38: 504–509.

13. Kwiecinski J, Jacobsson G, Karlsson M, Zhu X, Wang W, Bremell T, et al. Staphylokinase promotes the establishment of Staphylococcus aureus skin infections while decreasing disease severity. The Journal of Infectious Diseases. 2013; 208: 990–999.

14. Yagmurlu A, Barlas M, Gursel I, Gokcora IH. Reduction of surgery-induced peritoneal adhesions by continuous release of streptokinase from a drug delivery system. European Surgical Research. Europaische Chirurgische Forschung. Recherches Chirurgicales Europeennes. 2003; 35: 46–49.

15. Gemmill JD, Hogg KJ, Douglas JT, Dunn FG, Lowe GD, Rae AP, et al. The incidence and mechanism of hypotension following thrombolytic therapy for acute myocardial infarction with streptokinase-containing agents--lack of relationship to pretreatment streptokinase resistance. Eur Heart J. 1993; 14: 819-825.

16. Ko ATY, Teo Y, Teo HG, Cham YL. Factors and Outcomes Associated with Streptokinase-related Hypotension in Patients with ST Segment Elevation Myocardial Infarction (STEMI) in A Secondary Care Hospital in Malaysia. Int. J. Cardiol. 2019; 40: 16-17.

17. Pachaï A, Erlendsson AK, Brandslund I. Streptokinase, complement activation and hypotension. APMIS. 1997; 105: 650-654.

18. Lew AS, Laramee P, Cercek B, Shah PK, Ganz W. The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction. Circulation. 1985; 72: 1321-1326.

19. Wanda L Rivera-Bou. What is the mechanism of action for streptokinase in thrombolytic therapy? 2017.

20. Herlitz J, Hartford M, Aune S, Karlsson T. Occurrence of hypotension during streptokinase infusion in suspected acute myocardial infarction, and its relation to prognosis and metoprolol therapy. Am J Cardiol. 1993; 71: 1021-1024.

21. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2015; 36: 605–614.

22. Xu Q, Huang K, Zhai Z, Yang Y, Wang J, Wang C. Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: a meta-analysis. J Thorac Dis. 2015; 7: 810–821.

23. Goldhaber SZ. Venous thromboembolism: epidemiology and magnitude of the problem. Best Pract Res Clin Haematol. 2012; 25: 235–242.

24. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011; 123: 1788–1830.

25. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014; 35: 3033–3073.

26. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med. 2012; 125: 465–470.

27. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011; 123: 1788–1830.

28. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. Corrigendum to: 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2015; 36: 2642.

29. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005; 172: 1041-1046.

30. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016; 149: 315–352.

31. Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: a systematic review. Q J Med. 2013; 96: 103–113.

32. Weinberg I, Jaff MR. Accelerated thrombolysis for pulmonary embolism: Will clinical benefit be ULTIMAtely realized? Circulation. 2014; 129: 420–421.

33. Thabut G, Thabut D, Myers RP, Bernard-Chabert B, Marrash-Chahla R, Mal H, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol. 2002; 40: 1660–1667.

34. Dong B, Jirong Y, Liu G, Wang Q, Wu T. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2006.

35. Dong BR, Hao Q, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2009.

36. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004; 110: 744–749.

37. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Partha Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014; 311: 2414–2421.

38. Naidoo P, Hift R. Massive Pulmonary Thromboembolism and Stroke. Case Reports in Medicine. 2011.