# ACUTE MYOCARDIAL INFARCTION: A STUDY OF DOOR-TO-NEEDLE TIME OF THROMBOLYTIC THERAPY

BY

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# ABSTRAK

## SERANGAN JANTUNG AKUT: SATU KAJIAN JANGKAMASA DARI PINTU KEJARUM.


**OBJEKTIF**

Tujuan utama kajian ini adalah untuk menunjukkan kemungkinan untuk memulakan penggunaan Streptokinase di-dalam rawatan serangan jantung akut di Jabatan Kecemasan Hospital Kuala Lumpur dan juga hospital-hospital lain di negara ini.Tujuan kedua kajian ini pula, ialah ingin menunjukkan masa yang diambil untuk rawatan ini adalah lebih singkat sekiranya kita memulakan rawatan ini di jabatan kecemasan berbanding jika rawatan ini bermula di wad rawatan jantung, dan yang ketiga, untuk menunjukan masa yang diambil semakin singkat apabila kakitangan jabatan kecemasan sudah mempunyai pengalaman dengan cara rawatan ini..

## KAEDAH

Kajian ini telah dibuat pada tahun 1997, apabila semua pesakit dikenalpasti mengidap penyakit serangan jantung akut dirawat dengan menggunakan Streptokinase, di Jabatan Kecemasan Hospital Kuala Lumpur. Pada tahun 1997,

kami telah merawat seramai 67 orang pesakit dan pada tahun 1998 kami telah merawat seramai 66 orang pesakit sehingga bulan Julai sahaja.

Masa yang diambil untuk memulakan rawatan Streptokinase dikira bermula dari masa pendaftaran semua pesakit di jabatan kecemasan sehingga kami memulakan Streptokinase. Semua nama pesakit telah direkod oleh jururawat-jururawat di dalam buku pendaftaran khas. Semua kes- kes ini dirawat di zon kritikal jabatan kecemasan Hospital Kuala Lumpur sebelum dihantar ke wad rawatan jantung di tingkat empat. Selain merekod masa yang diambil, kami juga telah merekod nama, bangsa, jantina, dan umur para pesakit. Kami juga telah merekod komplikasi-komplikasi kaedah Streptokinase di jabatan kecemasan dan juga wad rawatan jantung (CCU).

Data tersebut telah dianalisa menggunakan ujian Fisher atau menggunakan ujian chi-square untuk membandingkan masa yang diambil pada tahun 1997 dan 1998. $p<0.05$ telah di ambil sebagai signifikan secara statistik.

**KEPUTUSAN**

Keputusan daripada kajian ini menunjukkan pengunaan Sreptokinase untuk pesakit serangan jantung akut boleh dimulakan di jabatan kecemasan.

Menurut kajian ini, keputusan yang diperoleh ialah:-

1. Masa yang diambil untuk memulakan streptokinase pada tahun 1997 iaitu selama 38 minit telah berjaya diperbaik pada tahun 1998 iaitu selama 26 minit sahaja. Ini adalah statistik signifikan dengan $p<0.05$

2. Pesakit serangan jantung lelaki adalah lebih ramai daripada pesakit serangan jantung perempuan. Terdapat 122 pesakit lelaki menakala pesakit perempuan hanya 11 orang dan peratusanya pula ialah 91.7% berbanding 8.3%.

3. Berbanding pesakit berbangsa Cina, pesakit berbangsa India adalah lebih ramai mengidap penyakit serangan jantung. Ini kerana, di Malaysia hanya terdapat 7% penduduk India dan peratusan kejadian serangan jantung ini adalah lebih tinggi, berbanding peratusan penduduk Melayu dan penduduk Cina yang mengidap penyakit yang sama.

4. Komplikasi yang paling banyak berlaku ialah gangguan perjalanan jantung dan diikuti pendarahan yang sedikit. Kami telah menyaksikan satu kematian yang berlaku serta-merta selepas streptokinase dimulakan. Walau bagaimanapun, tiada kejadian angin ahmar yang berlaku dalam kes-kes ini.

## KESIMPULAN

Berdasarkan keputusan kajian ini, berikut adalah beberapa panduan yang telah dicadangkan:-

1. Streptokinase boleh digunakan untuk merawat serangan jantung di jabatan kecemasan.

2. Adalah lebih baik untuk memulakan streptokinase di hospital daerah terlebih dahulu sebelum dirujuk ke hospital yang lebih besar.

# ABSTRACT


## ACUTE MYOCARDIAL INFARCTION : A STUDY OF DOOR-TO-NEEDLE TIME OF THROMBOLYTIC THERAPY

**OBJECTIVES**

The objectives of this study were firstly to show that it is possible to start thrombolytic therapy for acute myocardial infarction in the Emergency Department, Hospital Kuala Lumpur and probably in other emergency departments of other hospitals in the country. Secondly to show that the door to needle time is shorter if we were to start the thrombolytic therapy in the emergency department rather than in the coronary care unit ward. Thirdly that there would be an improvement in the door to needle time in the management of acute myocardial infarct in the emergency department once the staff of the department had more experience.

**METHODS**

The study in 1997, where all patients who were diagnosed as acute myocardial infarct were started on streptokinase except in cases during the admission days of Universiti Kebangsaan Malaysia, in which the permission was not given. In 1997 we had 67 patients and in 1998 we did the study until July as we had gathered 66 patients.

The door- to- needle time of starting thrombolytic therapy was calculated from the time of registration of the patients till the time the patient was started on streptokinase. All the names of the patients were recorded by the staff nurses in the special registration book specifically opened for these cases. All cases of acute myocardial infarction was treated and observed in the resuscitation zone in the Emergency Department Hospital Kuala Lumpur before being sent to the coronary care unit ward which is in the fourth floor of the hospital. Besides recording the door to needle time we also recorded the name, race, sex and age of the patients, We also recorded the early complications of the thrombolytic therapy in the emergency department and also when the patient is in the coronary care unit.

The data was analysed using Fisher's exact test or chi-square test comparing the door to needle time in 1997 and 1998 and statistical significance was taken as $p<0.05$.

## RESULTS

The results of this study showed that thrombolytic therapy for acute myocardial infarct could be started in the emergency department

From this study, it was found out that: -

1. The door to needle time was 38 minutes in 1997 and in 1998 it improved to 26 minutes. It was statistically significant with a p value less than 0.05.

2. Males outnumber females in the number of acute myocardial infarct.

   There were 122 male patients compared to 11 female patients and the percentage was 91.7% compared to 8.3%.

3. The number of patients of Indian origin with acute myocardial infarct was more compared to the Chinese. Comparing to the population of Malaysia, in which the Indians only comprised of 7% of the population, the incidence of acute myocardial infarct was relatively high compared to the Malays and the Chinese.

4. Complications did occur, the commonest was dysrthymia, followed by minor bleeding; we saw one death immediately after starting streptokinase. No stroke was seen in cases where we started streptokinase.

## CONCLUSION

Based on the results of this study, the following guidelines have been proposed: -

1. It is possible to start thrombolytic therapy in acute myocardial infarction in the emergency department.

2. It is better to start thrombolytic therapy in the smaller hospitals than transferring the case to bigger hospitals before starting thrombolytic therapy. This is to shorten the symptom-to-needle time.

# CHAPTER 1;- INTRODUCTION

Acute myocardial infarction is the most intensively studied medical intervention in the history of clinical investigations. In this study, besides comparing the door- to-needle time of starting streptokinase in the emergency department, discussion will be made on the current concept of acute myocardial infarction with regards to the epidemiology, anatomy, pathophysiology, therapeutics, diagnosis and the current management. In the diagnosis, which at times may be difficult, discussion will be made regarding electrocardiogram, biochemical markers and cardiac imaging that can be done at the emergency department. To understand better the overall picture of patient presenting with acute chest pain to the emergency department refer to the figure i.

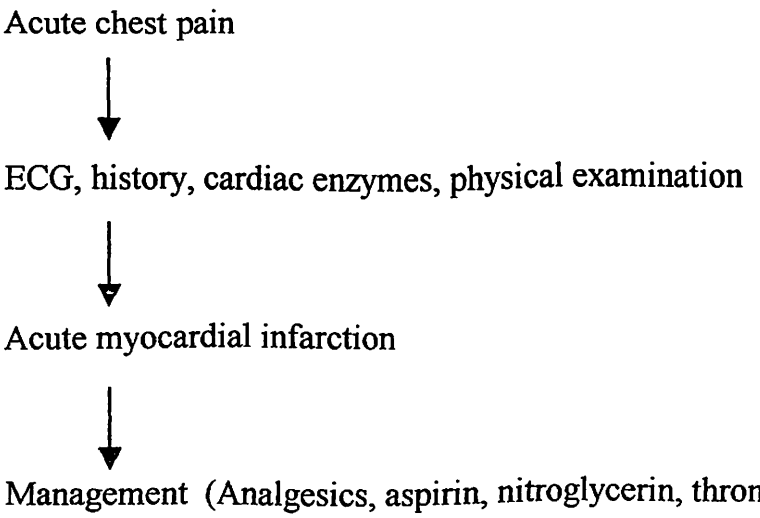


Figure i. General approach of patient presenting with acute chest pain in the emergency department.

The diagnosis of acute myocardial infarction depends on the typical history, ECG and cardiac enzymes or markers. To make the diagnosis of acute myocardial infarction, at least two out of the three of the above features must be present

The symptoms of ischemic heart disease include chest discomfort, often described as chest pressure, heaviness, tightness, fullness or squeezing. The classic location is substernal or in the left chest. Radiation to the arm and neck, or jaw may occur. In addition, the presence of associated symptoms such as nausea, vomiting, diaphoresis, dyspnea, light-headedness, syncope, and palpitations may be useful. The chest pain of acute myocardial infarction is more severe and prolonged usually more than 30 minutes. Atypical presentations or silent myocardial ischemia are common. Physical examination is not helpful in distinguishing patients with acute coronary syndromes from those with non cardiac chest pain syndromes. In the standard 12-lead ECG, the ST-segment is elevated in approximately 50% in acute myocardial infarction. (Braunwald E, et al, 1994, Jayes RL et al, 1992, Lee T, et al 1985). Most patients with acute myocardial infarction will have some nondiagnostic abnormalities on the ECG. (Lee T, et al, 1985). Some 1 to 5 percent of patients with acute myocardial infarction has an entirely normal ECG. (Lee T, et al, 1985,Selker HP, et al 1997,Slater DK, et al, 1987, Brush JE, et al, 1985). Newer cardiac enzymes or markers will play more prominent role in future, taking over the current "gold standard" of creatine kinase M- band (CK-MB). These includes troponin I and T and myoglobin when in combination will have greater specificity and sensitivity.

hour of symptom onset. It is disappointing therefore in the urban setting in Scotland that only 27% (GREAT Group 1992) of patients were admitted to the hospital within one hour of onset of symptom and is definitely worst in the rural settings. Using data from United Kingdom heart attack study, it has been estimated that 107per1000 (Sayer JW et al, 2000) lives were saved when they come to hospital within the first hour of symptom onset, compared with 21/1000 (J.W. Sayer et al, 2000) for those delayed more than 12 hours. As a strategy for saving lives, therefore early access to defibrillation is potentially more effective than from thrombolysis especially given that, in many centres only about 50% of patient with acute myocardial infarction are eligible for thrombolytic therapy.

To achieve the international standard of door-to-needle time of 60 minutes is almost impossible. The 60 minutes of door-to-needle time is used by the Australian Council on Healthcare Standards (ACHS) as a national clinical indicator. (Ralk E 1998). There are a number of difficult obstacles, which need to be tackled before we can achieve a target of 60 minutes. First and foremost, the patient must recognise, that the symptom is quite serious and he needs immediate attention. He or she needs transport to the nearest emergency department. It will save a lot of time if well-equipped ambulances are available immediately to transport and treat him on the way to the hospital. The paramedics in the ambulance must be able to treat the complications if it occur in the ambulance on the way to the hospital. In the emergency department, the staff must be able to triage him immediately to the resuscitation zone and streptokinase started immediately once the diagnosis of acute

myocardial infarction has been made and there in no contraindications of using streptokinase.

Previously the door- to- needle time was longer as the streptokinase can only be administered in the coronary care unit. In fact, studies that has been done in some hospitals in United Kingdom, showed that on the average, the door-to-needle time was about 80 minutes (Pell AC et al 1992). In this study in which, the streptokinase was started in the emergency department, the door-to-needle time was shorter and it would be shown that once the emergency department has started treating acute myocardial infarction with streptokinase the door to needle time could be reduced further. The current acceptable of door-to-needle time is 30 minutes and this can be reduced further to 15 minutes. This target could be achieved if the doctors and staff remain in the department, but this is not always the case, but continuous training and supervision must be continued with regards of administering streptokinase in acute myocardial infarction to all staff of the emergency department. The director of the hospital should monitor all the time. In Hospital Kuala Lumpur, the weekly report of the door-to-needle time was sent to him. (Appendix 2). The decision to start the thrombolytic therapy should be the responsibility of the doctors working in the resuscitation zone in the emergency department of the hospital and they should be a senior doctor, possibly a registrar. The emergency department should not depend on other departments to decide and start the streptokinase as they may not be available immediately.

The treatment for acute myocardial infarction should be started as soon as possible. To make it possible, the community must be educated with regard to the symptoms of acute myocardial infarction, and the need for the patient to be at the hospital as soon as possible. To educate the public is not difficult nowadays as the mass media, such as newspapers, radio, television and the internet can be used.

It is much better if the community can be provided with a well-equipped and efficient ambulance service, which can provide early treatment of acute myocardial infarction as well as starting the thrombolytic therapy. The ambulance should also be equipped with telemedicine service so that the paramedic can consult with the hospital staff if they encounter problems, which they cannot handle. Air ambulance if available can also cut down the time.

In Holland, (BMJ1998) the ambulance service does provide thrombolytic therapy at the patient home, and later transfer patient to the hospital. This is the best method to cut the time of starting thrombolytic therapy from the onset of symptoms. At the moment our ambulance service is not efficient and well-equipped compared to other developed countries. Hopefully, in a few years time we will have enough trained paramedic to run ambulances which should be well- equipped at the same time have telemedicine facilities which not only be able to treat acute myocardial infarct but any other serious illnesses.

Hospital Kuala Lumpur is among the first hospital in the world and in Malaysia to start thrombolytic therapy in the emergency department. The emergency department first started the treatment in 1997, but even then, it was late. In fact that the then Director-General of Health had proposed the administration of streptokinase, in the emergency department four years earlier but due to some unforeseen circumstances the emergency department were not able to start the service at the time.

Besides comparing the door-to-needle time between 1997 with 1998, we were also looking at the age, sex, and race of acute myocardial infarction patients. We were also looking at the complications that occur within the first few hours of treatment.

It is hoped with the result of this study, the Ministry of Health can be convinced that starting thrombolytic therapy in the emergency department is faster, effective and safe. We should start thrombolytic therapy in the emergency department of all major hospitals. If the thrombolytic therapy can be started in the emergency department in major hospitals, there is no reason why small district hospitals cannot start thrombolytic therapy in the hospital itself instead of sending such patients to the nearest bigger hospitals. This of course would certainly reduce the time in starting streptokinase in acute myocardial infarction, thus reducing morbidity and mortality.

# CHAPTER 2:- OBJECTIVES OF STUDY

The objectives of this study are firstly to show that it is possible to start thrombolytic therapy for acute myocardial infarction in the Emergency Department Hospital Kuala Lumpur. Secondly, to show that the door-to-needle time is reduced if the thrombolytic therapy is started at the emergency department rather than at the coronary care unit. Thirdly there will be an improvement of the door-to-needle time in the management of acute myocardial infarction in the emergency department once the staff becomes more experience. Fourthly, the complications that occur will be the same whether the thrombolytic therapy is started at the emergency department or at the coronary care unit. Finally we will be able to identify the sex, age, race and early complications of patients suffering from acute myocardial infarction at the emergency department.

# CHAPTER 3:- LITERATURE REVIEW

## 3.1 EPIDEMIOLOGY

Coronary artery disease (CAD) is the number one killer in Malaysia. Thirty per cent of medically- related deaths reported in the country in 1998 were caused by cardiovascular disease. Statistics showed that 82,356 patients were warded in government hospitals in 1998 for cardiovascular problems compare to 58,838 ten years previously. There were also 4,248 deaths due to the disease in 1998 compared to 4,059 in 1988. (Ministry of Health of Malaysia).

Global statistics supplied by World Health Organization (WHO) indicates that CAD is by far the major killer in almost all developed countries, and emerging major problem amongst developing nations. Heart disease has emerged as one of the world's biggest killers. It is the main cause of death in developed countries and by the year 2020 it is expected to be the leading cause of death in developing countries as well (New Sunday Times, 18.9.2000).

As observed by the World Heart Federation " CAD is a disease without geographic, gender or socio-economic boundaries ". Heart disease is largely preventable and controllable. Worldwide ischaemic heart disease is believed to cause around 6.3 million deaths annually. Ischaemic heart disease is the leading cause of

death in United Kingdom and the United States of America. Over 6 million United State citizens have coronary artery disease. There are 4 to 5 million emergency department visits for acute chest pain annually in USA. Coronary artery disease results in approximately 500,000 deaths annually in the USA (Clinical Medicine, 1998). The total economic bills are around $100 billion per year. In fact in United Kingdom the mortality from coronary heart disease is falling. (British Heart Foundation Coronary Heart Disease Statistics 1999). Death is being postponed, not prevented .Coronary heart disease will continue to increase up to the year 2020. (Murray CJL, Lopez AD 1997).

In Malaysia, there is a high prevalence rate of Malaysian of Indian origin to have coronary artery disease compared to the Malays and the Chinese. In fact, Indians has 1.5 times incidence of ischaemic heart disease compared to the Malays (Khoo K.L et al 1991). A higher incidence of ischaemic heart disease has also been found in Asian Indians in other parts of the world (Heng et al 2000) .It is attributed to the difference in prevalence of risk factors in different races such as diabetes mellitus, increase in insulin resistance, central obesity and lower low -density lipid.

## 3.2 ANATOMY

Knowledge of the anatomy of the coronary artery is essential to understand the effects of myocardial ischemia and why some complications are more common with anterior or inferior wall myocardial infarct. The left coronary artery arises from

the ascending aorta in the left sinus of the aortic valve. It courses through atrioventricular sulcus on the left side, and divides into left circumflex and left anterior descending branch. The left anterior descending branch courses down the anterior aspect of the heart around the inferior margin and anastomoses with the posterior diagonal branch of the right coronary artery. It is the main blood supply to the anterior and septal region of the heart. The circumflex branch continues around the atrioventricular sulcus, where it anastomoses with the right coronary artery. It supplies to some of the anterior wall and a large portion of the lateral wall of the heart. The right coronary artery arises from the right sinus of the aortic valve and runs in the atrioventricular sulcus between the right atrium and the right ventricle. It gives off a marginal branch near the lower aspect of the heart and terminates as right posterior descending artery .The right coronary artery supplies the right side of the heart with blood and it provides some perfusion to the inferior aspect of the left ventricle through the posterior descending artery.

The Atrio-Ventricular (AV) conduction system receives blood supply from the branch of the right coronary artery and the septal perforating branch of the left anterior descending artery, Similarly, both the right bundle branch and the left posterior division obtain a dual blood flow from the left anterior descending and right coronary artery.

## 3.3 PHYSIOLOGY

Hypoxia is the reduction of oxygen supply to the tissue despite adequate perfusion. Ischemia occurs when there is imbalance between oxygen demand and oxygen supply. Oxygen supply is influenced by the oxygen carrying capacity of the blood and the coronary artery blood flow. The oxygen carrying capacity of the blood is determined by the amount of hemoglobin present.

Coronary artery flow is determined by the diastolic relaxation of the heart and vascular resistance. Humoral, neural, metabolic, extravascular compressive forces and local autoregulation make up the coronary vascular resistance.

The platelet response involves adhesion, activation and aggregation. Platelet adhesion occurs through the weak platelet interaction with subendothelial adhesion molecules such as collagen, fibronates and laminin and the binding of glycoprotein 1b receptors to the subendothelial form of von Willebrand factor. Adherent platelets are strongly thrombogenic . Lipid- laden macrophages in the plaque core and the adventitia of the vessel wall release tissue factor, which stimulates the conversion of prothrombin to thrombin. Thrombin, collagen, and the local shear forces are all potent platelet activators. Platelet secretes adenosine diphosphate, thromboxane H two and serotonin are autostimulating agonist of platelet activation. Activated platelet glycoprotein IIb/IIIa receptors become cross-linked by fibrinogen on von-Willebrand factor in the common pathway of platelet aggregation.

## 3.4 THE PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME

The thrombosis developing on a culprit coronary atherosclerotic plaque causes virtually all-regional acute myocardial infarcts. The very rare exceptions are coronary artery dissection, coronary arteritis, coronary emboli, coronary emboli, coronary spasm and compression by myocardial bridges. Thrombus is also the major initiating factor in unstable angina, particularly when rest pain is recent and when the pain isincreasing in severity. Necropsy studies, suggest that a new thrombotic coronary event underlie 50 to 70% of sudden death caused by ischemic heart disease. (Davies MJ 1992).

The fully-developed human fobrinolipid plaque designated by American Heart Association (AHA) as type IV or type Va has a core lipid surrounded by a capsule of connective tissue. The core is an extracellular mass of lipid containing cholesterol and its esters. The core is surrounded by numerous macrophages, many of which contain abundant intracystoplasmic droplets of cholesterol (foam cells). These macrophages are not inert but are highly activated producing procoagulant tissue factor and a host of inflammatory cell mediators such as tumour-necrosing factor alpha, interleukins and metalloproteinases, (Stary H, et al, 1995).

The early stages of plaque development (AHA type I-III) are not associated with evidence of structural damage to the endothelium. Once the plaque formation

has progress to stage IV, however structural changes in the endothelium become almost universal. Focal areas of endothelium denudation occur over the plaque, exposing the underlying connective tissue matrix and allowing a monolayer of platelet to adhere to the site.

Thrombosis over plaque occurs because of two somewhat different processes. One is caused by an extension of the process of endothelial denudation, so that large areas of the surface of the subendothelial connective tissue of the plaque are exposed. Thrombus forms and it is adherent to the plaque surface. This process has become known as endothelial erosion. The macrophages are highly activated and cause endothelial cell death by apoptosis and also by the production of proteases, which cut loose the endothelial cells from their adhesion to the vessel wall.

The second mechanism for thrombus formation is plaque disruption (rupture fissuring) where the plaque cap tears to expose the lipid core to blood in arterial lumen. The core areas are highly thrombogenic containing tissue factors, fragment of collagen and crystalline surfaces to accelerate coagulation. Thrombus forms initially in the plaque itself, which expanded and distorted from within; the thrombus may then extend into arterial lumen.

Plaque disruption like endothelial erosion is a reflection of enhanced inflammatory activity within the plaque. The cap is a dynamic structure within which the connective tissue matrix, upon which its tensile strength depends, is constantly

being replaced and maintained by the smooth muscle cell. The inflammatory process both reduces collagen synthesis by inhibiting the smooth muscle cell and causes its death by apoptosis. Macrophages also produce a wide range of metalloproteinases capable of degrading all the component of the connective tissue matrix, including collagen. These metalloproteinases are secreted into the tissues in an inactive form and then activated by plasmin. Metalloproteinase production by macrophages is upregulated by inflammatory cytokines such as tumour-necrotising factor alpha. Plaque disruption is therefore now seen as an auto-destruct phenomenon associated with an enhanced inflammatory activation.

The relative importance of disruption and erosion as triggers of thrombosis may vary from between different patient groups. Disruption is the prodominant cause (>85%) of major thrombi in white males with high plasma cocentrations of low density lipoprotein(LDL), and low concentration of high density lipoprotein (HDL). In contrast, in women endothelial erosion is responsible for around 50% of major thrombi. The distinction between erosion and disruption, is not necessary of major clinical importance. Both processes depend on enhanced inflammatory activity within the plaque and appear equally responsive to lipid lowering. Disruption has an intraplaque component more resistant to fibrinolytic treatment, while in erosion the thrombus is more accessible. This potential advantage is, however, offset by erosion related thrombi tending to occur at sites where the pre-existing stenosis was more severe. In women there is also a form of thrombosis caused by endothelial erosion over plaques, which do not contain lipid or major inflammatory component. This

type of disease is rare and arguably distinct from conventional atherosclerosis, and may be smoking related. (Burke A et al 1997, Davies M, 1997,Arbustini E et al 1999).

Analysis of plaque, which has undergone disruption has been used to determine characteristics which may indicate currently stable plaque whose structure and cell content makes them likely to undergo thrombosis in the future (vulnerable plaques).

There is widespread unanimity in the belief that these features are:

1. A large lipid core occupying at least 50% of the overall plaque volume
2. A high density of macrophages
3. A low density of smooth muscle cells in the cap.
4. A high tissue factor content
5. A thin plaque cap in which the collagen structures is disorganised.

All of these markers of plaque at future risks are likely to be the direct results of macrophages activity, which enlarges the core and thins the cap. (Davies M 1997).

The risk of any subject with coronary artery disease having a future acute event will depend on the number of these vulnerable plaque, which are present, rather than on the total number of plaques. Patients, however, vary in the number of vulnerable plaques, which are present in the coronary arteries. This variation

explains why one individual has a series of infarcts at regular intervals while another individual has an infarct without further events for the next 10 to 20 years.

The thrombi, which occur either in disruption or erosion circumstances, are dynamic and evolve in stages. In disruption, the initial stage occurs within the lipid core itself and is predominantly formed of platelets. As thrombus begins to protrude in the lumen, the fibrin component increases, but any surface exposed to the blood in the lumen will be covered by activated platelets and are swept down into the distal intramyocardial arteries as microemboli. Thrombus may grow to occlude the arteries leading to a final stage in which there is a loose network of fibrin containing a large number of entrapped red cells. The third and final stage thrombus may propagate distally after the onset of myocardial infarction. The final stage of occlusive thrombus has a structure making it very susceptible to either natural or therapeutic lysis, but expose the deeper and earlier thrombus, which is more resistant to lysis.

Episodes of plaque disruption, which are almost entirely associated with intraplaque thrombus, are associated with the onset of exacerbation of stable angina caused by sudden increase of plaque volume. Thrombi, which project into but do not occlude the lumen (mural thrombi), are the basis of unstable angina. The intermittent attacks of myocardial ischemia at rest are caused by several potential mechanisms. The thrombus may intermittent wax and wane in size and become occlusive for short periods of time.

There may be intense local vasoconstriction. Many disrupted plaques are eccentric, with the retention of an arc of normal vessel wall in which constriction can reduce blood flow. Platelet deposition is a known potent stimulus for local smooth muscle constriction. Embolisation of platelet aggregates into the intramyocardial vascular bed both block smaller arteries in the size range of 50-100um external diameter and cause vasoconstriction within the myocardium. Necropsy studies show a strong correlation between such platelet thrombi and microscopic foci of myocyte necrosis. It is difficult now to perceive why coronary thrombosis was regarded 25 years ago as an inconstant and irrelevant consequence of acute infarction rather than its prime cause. Once angiography was carried out soon after the onset of infarction, and it was realised that the subtending artery was totally blocked but spontaneously reopened with time in many cases (and that this reopening was accelerated by fibrinolytic treatment ), thrombosis was seen as a major causal factor in occlusion. Suddenly, the clinical world found thrombi to be both dynamic and important. Pathologists had thought that thrombi was important but did realise how dynamic it could be. Sequential angiograms taken over some years in patients which chronic heart ischaemic disease also changed perceptions. It was realised that a significant proportion of thrombotic occlusion causing infarction did not develop at sites where there was pre-existing high-grade stenosis, or even a plaque identified at all. Sixty-eight percent of the occlusions leading to acute infarction were judged to have caused less than 50% diameter stenosis previously, while only 14% developed on high grade stenosis of more than 70% diameter in a recent review of literature. (Falk E, et al, 1995).

The advent of intravascular ultrasound has confirmed that many stable coronary plaques angiograpically invisible because of arterial remodelling. In this process, described so well by Glacov, the artery is seen to respond to plaque growth by increasing its cross sectional area while retaining normal lumen dimensions. Angiography cannot and does not predict the sites and risk of future infarctions. It is true that chronic high-grade stenoses do progress to occlude, but this is a slow process and is often caused by erosion type thrombosis and is not associated with acute infarction due to collateral flow. For example, 24% of lesions occluding more than 80% by diameter will progress to chronic total occlusion by five years. (Glagov S, Weisenberd E, Zarins C, et al 1987).

The magnitude of episodes of disruption varies widely. At one extreme, the plaque has a crack or fissure only, and the large thrombotic response appears out of proportion to the stimulus. Such events are easily treated by lysis to give a lumen size, which is a little different from the previous state or event taken to be a normal artery. At the other extreme, a plaque undergoes complete disintegration, occluding the lumen with a plaque content and thrombus. Another form is where the artery is occluded by the thrombus expanding the plaque from within. These more complex types of disruption occlusion will be more likely to respond to primary angioplasty. The exact morphology of disrupted plaque causing occlusion cannot, however, be determined in vivo by any current methodology.

Transmural regional acute myocardial infarction is caused by a coronary artery occlusion, which develops over a relatively short time frame of a few hours and persists for at least 6-8 hours. The infarcted tissue is structurally suggestive of homogenous entity-that is, all the myocardium involved died at around the same time. Non-transmural regional infarcts (non-Q wave} have a different structure which is built up by the coalescence of many small areas of necrosis of different ages. This pattern of necrosis characteristically follows crescendo unstable angina and appears to be caused by repetitive episodes of short-lived occlusion or platelet embolisation or both. A further factor in limiting the spread of necrosis and preserving the subpericardial zone is the existence of prior collateral flow in the affected artery. (Braunwald E 1998).

The challenge of understanding pathophysiology of unstable angina is the wide spectrum of clinical severity. Necropsy studies are inevitably biased toward the worst outcome, but within this limitation show unstable angina to be caused by disrupted plaques with exposed mural thrombi and retention of antegrade flow in the artery. This feature of some antegrade flow is all that separates the vascular lesion of unstable angina from that of acute infarction. The persistence of the thrombotic process so that it neither progresses to occlude nor resolves to heal represents a balance between prothrombotic and antithrombotic factors. Confirmation of plaque disruption and thrombosis as the basis of severe unstable angina has come from angiography in vivo where type II lesions with irregular overhanging edges and intraluminal filling effects representing thrombus is found. These angiographic

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appearances are rare in unstable angina. Type II lesions have been shown to be disrupted plaques by pathology studies. Angioscopy has directly observed torn plaque cap in vivo and intravascular ultrasound has also identified disrupted plaque in vivo. Atherectomy studies comparing tissue from plaque thought to be responsible for stable and unstable angina have shown very consistent results.

## 3.5 ELECTROCARDIOGRAM (ECG)

The normal myocardium depolarizes from endocardium to epicardium and repolarises in the opposite direction. When injured, the myocardium remains electrically more positive than the uninjured part at the end of depolarisation. The relatively positive potential in this area will result in ST elevation of the ECG leads over this area. Conversely, if the electrode is located over the uninjured myocardium opposite the injured area ST depression will be noted (reciprocal changes).

After acute myocardial infarct the area of necrosis is electrically silent. The resultant forces generated from the myocardium during repolarisation (the QRS complex) will be affected by the electrically silent area. Electrodes facing the infarcted area will record and abnormal negative deflection during depolarisation (pathological Q-waves).

The standard 12-lead ECG, is the single best test to identify patient with acute myocardial infarction upon emergency department presentation. American National guideline requires that it be obtained and interpreted within 10 minutes of presentation. Although, it is been immediately available test in the emergency department, it stills has relatively low sensitivity for the detection of acute myocardial infarct. (Lee T, Cook F, Weisberg M et al, 1985).

The ST-segment is elevated during acute myocardial infarction in approximately 50% i.e. half of the patients who presented to the emergency department with acute myocardial infarct would not be detected solely on the basis of ECG. Many patients with acute myocardial infarct will have some non-diagnostic abnormalities in the ECG. Some 1% to 5% of patient with acute myocardial infarct has an entirely normal ECG. These figures refer to myocardial infarct, not to angina. (Brush JE, et al 1985).

ST-segment elevation in the distribution should suggest acute transmural injury. All inferior waves myocardial infarct should have a right-sided V4 (rV4) obtained because ST-segment elevation in rV4 is highly suggestive of right ventricular infarct. In general the more elevated the ST-segments and the more ST-segments that are elevated, the more extensive the injury is.

The ECG can also be used to predict the infarct- related vessels. Inferior wall infarction can result from occlusion of the left circumflex artery or the right coronary

artery. In the setting of an inferior wall infarction, ST-segment elevation in at least one lateral leads (V5, V6, aVL) with an isoelectric or elevated ST-segment in lead I is strongly suggestive of left circumflex lesion. The presence of ST-segment elevation in lead III greater then that of lead II predicts a right coronary artery occlusion. When accompanied by either ST-segment elevation on V1 or aVR it predicts a proximal a right coronary artery occlusion with accompanying right ventricular infarction. Reciprocal anterior ST- segment depression in V1 through V4 is equally prevalent in both.

The main utility of the ECG is to detect acute myocardial infarction. The admission ECG, although excellent for selecting patients for thrombolysis, has a diagnostic sensitivity of acute myocardial infarct of 55-75 %. The standard 12-lead ECG is useful in cardiovascular risk stratification of patient with acute coronary syndromes. It can be used in conjunction with clinical history and cardiac markers to determine admission location for such patients. (Lee T, et al 1985).

Novel approaches to the ECG have been proposed in the last decade. A continuous 12-lead ECG has been developed that record a new 12-lead ECG monitor every 20 seconds. When ST-segment baseline is altered, an alarm is raised and a copy of the new ECG is automatically showed or printed. This type of technology might be useful for monitoring patients who present with non-acute myocardial infarct, acute coronary syndrome for ECG evidence of injury. Because of the cost

concern regarding labile ST- segment and T-wave changes from hyperventilation or patient movements and lack of Emergency Department based prospective studies, continuous 12-lead ECG monitoring has not been recommended for routine used. ECG with 15,18 and 22 leads have been studied. The addition of V4R, V8, and V9, increased sensitivity without loss of specificity for the detection of ST segment elevation. The addition of V4R through V6R and V7-V9 may lead to increase sensitivity but at the cost of decrease specificity.

There are several clinical conditions where ECG interpretation is difficult. It has been shown that in the setting of paced rhythms and the left bundle branch block, acute myocardial ischemia can be identified. In the setting of left bundle branch block (LBBB), the presence of ST- segment elevation >- 1mm and concordant with QRS complex ST segment depression> 1mm in lead V1, V2 or V3 suggest acute myocardial infarct. ST- segment elevation >5mm and discordant with the QRS complex increase the likelihood of acute myocardial infarct, but has poor specificity. Any ST segment elevation concordant to the QRS complex predominantly the QRS complex was highly specific for acute myocardial infarct, the QRS complex is predominantly negative in leads V1 to V3. ST segment depression in the leads has 80% specificity for acute myocardial infarct. (Sgarbossa EB, et al 1996).