HYPERLACTATEMIA AS PREDICTOR MORBIDITY IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Acute myocardial infarction (AMI) still have high prevalence of morbidities and mortality, and therefore we need a reliable marker that represent the severity of the disease. Degree of hypoperfusion can measure by lactate production. Lactate is a byproduct of anaerob metabolism and marker of tissue hypoperfusion.The prognostic role of lactate for morbidity in patients with AMI has not been elucidated so far. There is no previous study to determine the role of hyperlactatemia as predictor of morbidity in AMI patients in Indonesia.The aim of this study was to assess whether lactate is an independent prognostic predictor morbidity patient with AMI in Sanglah Hospital, Denpasar. This was an observational cohort prospective study, which enrolled 70 AMI patients by consecutive sampling. We measured capillary lactate level three times, at first admission, 2h, and 24 h after admission, using rapid point-of-care analyzer accutrend lactatemeter. We observed for morbidities and the subsets (cardiogenic shock, heart failure, arrhythmia) during hospitalization. The result of this study were the AMI patients with hyperlactatemia have an almost 3-fold [hazard ratio (HR) =2.578,95%confidence interval (CI)=1.278 to 5.199, P=0.008)increased risk of morbidity, a 15-fold increased risk ofcardiogenic shock of(HR =15.231, 95% CI =1.848 to 700.579,P=0.0014) and a 5-fold increased risk of heart failure (HR=5.269, 95% CI =1.913 to 15.796,P=0.0002) compared with subject without hyperlactatemia. On the other hand, hyperlactatemia was not associated as a predictor of arrhythmia (HR = 1.35, 95% CI = 0.344 to 4.627,P=0.3051).Hyperlactatemia is an independent predictor of morbidity, cardiogenic shock, and heart failure in AMI patients. On the other hand, hyperlactatemia is not an independent predictor of arrhythmia in AMI patients. **[MEDICINA 2015;46:71-6].**

Keywords: *acute myocardial infarction, hyperlactatemia*

HIPERLAKTASEMIA SEBAGAI PREDIKTOR MORBIDITAS PADA INFARK MIOKARD AKUT

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ABSTRAK

Prevalensi morbiditas dan mortalitas pada infark miokard akut (IMA) masih cukup tinggi, dengan demikian dibutuhkan biomarker yang reliabel menggambarkan keparahan penyakit. Derajat hipoperfusi dapat dinilai dengan mengukur produksi laktat.Laktat merupakan produk metabolisme anaerob dan penanda hipoperfusi jaringan. Peran laktat sebagai prognosis morbiditas pada pasien IMA hingga saat ini belum diketahui. Hingga saat ini belum ada studi untuk menentukan peran hiperlaktasemia sebagai prediktor morbiditas IMA di Indonesia. Studi ini dilakukan untuk menilai apakah laktat sebagai prediktor independen prognosis morbiditas pasien IMA di Rumah Sakit Sanglah, Denpasar. Penelitian ini merupakan studi observasional kohort prospektif yang melibatkan 70 pasien IMA dengan cara konsekutif. Dilakukan tiga kali pemeriksaan kadar laktat kapiler secara serial yaitu saat pertama kali masuk rumah sakit, 2 jam, dan 24 jam setelahnya dengan menggunakan alat analisis cepat *accutrend lactatemeter*. Selama perawatan diamati adanya morbiditas, syok kardiogenik, gagal jantung, dan aritmia. Pada penelitian didapatkan hiperlaktasemia pada pasien IMA merupakan prediktor morbiditas risiko hampir 3 kali lipat (HR =2,578,IK 95% = 1,278 sampai 5,199, P=0,008), prediktor syok kardiogenik sebesar 15 kali lipat (HR =15,231, IK 95% = 1,848 sampai 700,579,P=0,0014) dan prediktor gagal jantung 5 kali lipat (HR=5,269, IK 95% = 1,913 sampai 15,796,P=0,0002) dibandingkan pasien tanpa hiperlaktasemia. Hiperlaktasemia tidak terbukti sebagai prediktor aritmia(HR = 1,35, IK 95% = 0,344 sampai 4,627, P=0,3051).Hiperlaktasemia merupakan prediktor independen morbiditas, syok kardiogenik, dan gagal jantung pada pasien IMA. Hiperlaktasemia tidak terbukti sebagai prediktor independen aritmia pada pasien IMA. **[MEDICINA 2015;46:71-6].**

Kata kunci :*infark miokard akut, hiperlaktasemia*

INTRODUCTION

Coronary artery disease (CAD) is a worldwide epidemical problem. Estimated mortality caused by CAD about 30%. Acute myicordial infarction (AMI) still has prevalent burden of morbidities.[1] Emergency physicians are keenly aware of thelimitations of present laboratory investigations, particularly in the early phases of an AMI. The initial electrocardiogram (ECG) is exclusively diagnostic in only about 50% of AMIs. Biochemical markers, including levels of creatine kinase (CK), CK-MB, and the troponins, are often within normal range initially and may take up to six to 12 hours to rise to a diagnostic level.Myoglobin level has an earlier rising, but its lower specificity makes it a less useful test in the emergency department(ED).[1,2] Most of laboratory tests like CK-MB, troponins, and myoglobin mainly depends on cellular damage due to ischemia and release amount of intracellular enzymes into the circulation. These parameters are not fully explains the measurement of physiological disturbances level of the heart. Therefore these parameters only have low sensitivity before 4-6 hours after ischemia onset and not practical in the management of acute chest pain.[1-3] Lactate is increased in physiological disturbance of the heart and quite sensitive in diagnosing AMI. This early rise of lactate were observed within 2 hours of chest pain onset.[3,4] Lactic acid is a byproduct of anaerobic glycolysis that rises in state of tissue hypoperfusion, and quickly buffered into lactate in the circulation. States of regional hypoperfusion frequently occur in AMI, despite maintenance of normal blood pressure. In addition, under basal conditions, the myocardium extracts lactate from the circulation, but in conditions of cardiac ischemia, its ability to do so is compromised. Therefore, myocardial ischemia could cause an elevation in the level of circulating lactate through both of these mechanisms.[3,5]

Several studies have been done to assess the effect of hyperlactatemia on mortality. However, there was no study determine the effect of hyperlactatemia on morbidity in patient with acute myocardial infarction. This study was conducted to determine lactate as a predictor of morbidities in AMI. The hypothesis was hyperlactatemia can be used as predictor of morbidities in AMI. If proven, lactate could be used to stratify, prognostic assessment and monitoring properties in AMI patients.

METHODS

This was an observational cohort prospective study conducted from July until September 2014, with 70 consecutive AMI patients in Sanglah Hospital. All patients with chest pain are first evaluated in emergency department. Diagnosis of AMI was based on WHO criteria. Patient with heart failure, chronic kidney disease, chronic liver disease, sepsis, diabetic ketoacidosis, cancer, HIV on antiretroviral treatment were excluded, because lactate levels have been shown to be considerably elevated in this subset patient.

Lactate levels were obtained simultaneously on a single capillary puncture sample using the accutrend lactate meter, ahandheld, battery-powered reflectance photometer manufactured by Roche Diagnostics, Mannheim, Germany.

Accutrend lactate meter using light emitting diode (LED) to measure colour in test strip during reaction then compare with baseline (enzymatic photometric measurement). Lactate was measure three times at first time contact, 2 hour, and 24 hour after admission. The highest lacate level from three times measurement was analyzed. We observed-morbidity as the primary outcome and the subsets (cardiogenic shock, heart failure, and arrhythmia) until the patient was discharged from hospital.A medical record patient was used to collect information on cardiovascular risk factors.

All data were analyzed using stata E 12. Cutt of point to determine hyperlactatemia in order to predict morbidity visualized by receiver operating characteristic (ROC). The study population was divided into two groups based on cutt of point hyperlactatemia. Where appropriate, independent t-test, non-parametric test (two group mean comparison test), chi-square tests were used to make comparisons among the two groups of patients. Data are reported as frequencies (percentages) and medians (95% CI).

To calculate multivariate relations of lactate and other baseline characteristics that were available before the first admission to morbidity and the subset (cardiogenic shock, heart failure, arrhythmia), we used binary logistic regression analysis. Lactate was entered into the analysis as a continuous variable after log normal transformation. To calculate differences morbidity, cardiogenic shock, heart failure, and the presence of arrhythmia between the two groups in Kaplan-Meiercurves we performed a logrank test (Mantel-Cox.). AP-value of d"0.05 was considered statistically significant. By means of 2 multivariable backward linear regression analyses, we explored the adjusted correlations of lactate with clinical and biochemical variables, the respective final models have beenreported. Logistic regression analysis was carried out considering as outcomes morbidity. This study approved by Ethics Committee of Udayana University Medical School/Sanglah Hospital Denpasar.

RESULTS

A total of 70 patients were included from July-September 2014. The main diagnosis of the 70 patient with AMI is ST elevation myocardial infarction (STEMI) (68.6%), Non-ST elevation myocardial infarction (NSTEMI) (31.4%). Patient characteristics for the study population are given in **Table 1**. Patient was categorized into two group based on the presence of hyperlactatemia. The ROC curve to determined hyperlactatemia as predictor morbidity is presented in **Figure 1**.

Table 1. Patient's characteristics

Characteristics	Total (N=70)	Hyperlactatemia	
		Yes (N=23)	No (N=47)
Demography, n(%)			
Man	63 (90)	18 (78.26)	45 (95.74)
Woman	7(10)	5 (21.74)	2 (4.26)
Age (year), mean (SD)	57.9 (11.5)	58.1 (13.3)	57.7 (10.6)
Presenting characteristics			
Onset chest pain, n(%)			
<12 hour	48(68.57)	14 (60.87)	34 (72.34)
>12 hour	22 (31.43)	9 (39.13)	13 (27.66)
Diagnosis, n(%)			
STEMI	48 (68.57)	18 (78.26)	30 (63.83)
NSTEMI	22 (31.43)	5 (21.74)	17 (36.17)
Laboratorium result, n(%)			
CKMB			
≤40 IU/mL	52 (74.29)	14 (60.87)	38 (80.85)
>40 IU/mL	18 (25.71)	9 (39.13)	9 (19.15)
Troponin, n(%)			
≤2000 ng/mL	53 (75.71)	18 (78.26)	35 (74.47)
>2000 ng/mL	17 (24.29)	5 (21.74)	12 (25.53)
Hemoglobin(mg/dL), mean (SD)	13.9 (2.2)	13.8 (2.9)	14.1 (1.8)
pO_2(mmHg), mean(SD)	138.5 (38.8)	140.3 (39.7)	137.6 (38.7)
Albumin(g/dL), mean (SD)	3.7 (0.5)	3.7 (0.6)	3.7 (0.4)
Random blood sugar (mg/dL), mean (SD)	172 (80.2)	144.7 (49.2)	186.6 (88.9)
Cardiovascular risk factor			
Family history, n(%)			
Yes	8 (11.43)	4 (17.39)	4 (8.51)
No	62 (88.57)	19 (82.61)	43 (91.49)
Dyslipidemia, n(%)			
Yes	21 (30)	4 (17.39)	17 (36.17)
No	49 (70)	19 (82.61)	30 (63.83)
Hypertension, n(%)			
Yes	32 (45.71)	11 (47.83)	21 (44.68)
No	38 (54.71)	12 (52.17)	26 (55.32)
Diabetes, n(%)			
Yes	21 (30)	4 (17.39)	17 (36.17)
No	49 (70)	19 (82.61)	30(63.83)
Smoking, n(%)			
Yes	45 (64.29)	11 (47.83)	34 (72.34)
No	25 (35.71)	12 (52.17)	13 (27.66)
Treatment reperfusion, n(%)			
Yes	29 (41.43)	8 (34.78)	21 (44.68)
No	41 (58.57)	15 (65.22)	26 (55.32)

The ROC curve of for lactate level to determine hyperlactatemia.The curve showed cut off point 3 mmol/L as the best value to determined hyperlactatemia. Area under the curve is significantly different to the null hypothesis value.

Effect of hyperlactatemia to morbidity and the subsets (cardiogenic shock, heart failure, and arrhythmia) was showed by estimates Kaplan Meier Survival Curve as in **Figure 2**. To determine the difference of probability survival we used Log rank test.

Hyperlactatemia predicts morbidity in patient with AMI of almost 3-fold [HR =2.578(95% CI=1.278 to 5.199), P=0.008], cardiogenic shock of 15-fold [HR =15.231 (95% CI =1.848 to 700.579),P=0.0014] and heart failure of 5-fold [HR=5.269 (95% CI =1.913 to 15.796),P = 0.0002] compared with subject without hyperlactatemia. On the other hand, hyperlactatemia was not proved as the predictor of arrhytmia [HR = 1.35 (95% CI = 0.344 to 4.627), P=0.3051].

To assess effect hyperlactatemia as predictor morbidity in subgroup infarction (STEMI and NSTEMI) we used Mantel Haensel analysis. Effect of hyperlacatatemia to morbidity in STEMI patient is 3.8 times (P=0.0009, 95% CI : 1.539 to 9.68), meanwhile in NSTEMI patient this effect about 5.2 times (P= 0.0131, 95% CI: 1.032 to 24.159). There was difference effect in both subgrup.

In multivariate analysis, we determined if clinical characteristics and risk factors readily available at presentation (sex, education, dyslipidemia, diabetes, smoker, diagnosis, CKMB, and blood sugar) were

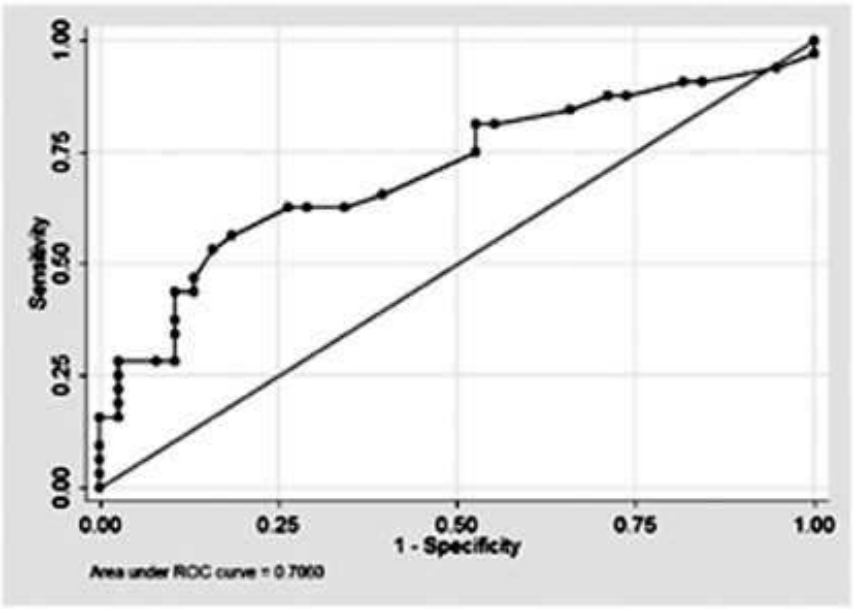

Figure 1. ROC curve to determined hyperlactatemia. Area under the curve 0.706, standard error 0.0647, 95% CI 0.579 to 0.833.

independently related to morbidity. **Table 2** shows the strength of each independent relation and the level of significance.

From overall 8 independent variables, only 2 which is dyslipidemia and CKMB changes HR more than 10% but with P>0.05.

DISCUSSION

Sustained hyperlactatemia has been shown to be predictive for adverse outcome in a number of studies, and therefore serial lactate measurements might be a useful approach to monitor the critically ill patient. Another advantage by using serial measurements is that patients having a temporary and non-pathologically elevated lactate, for instance as a result of a high

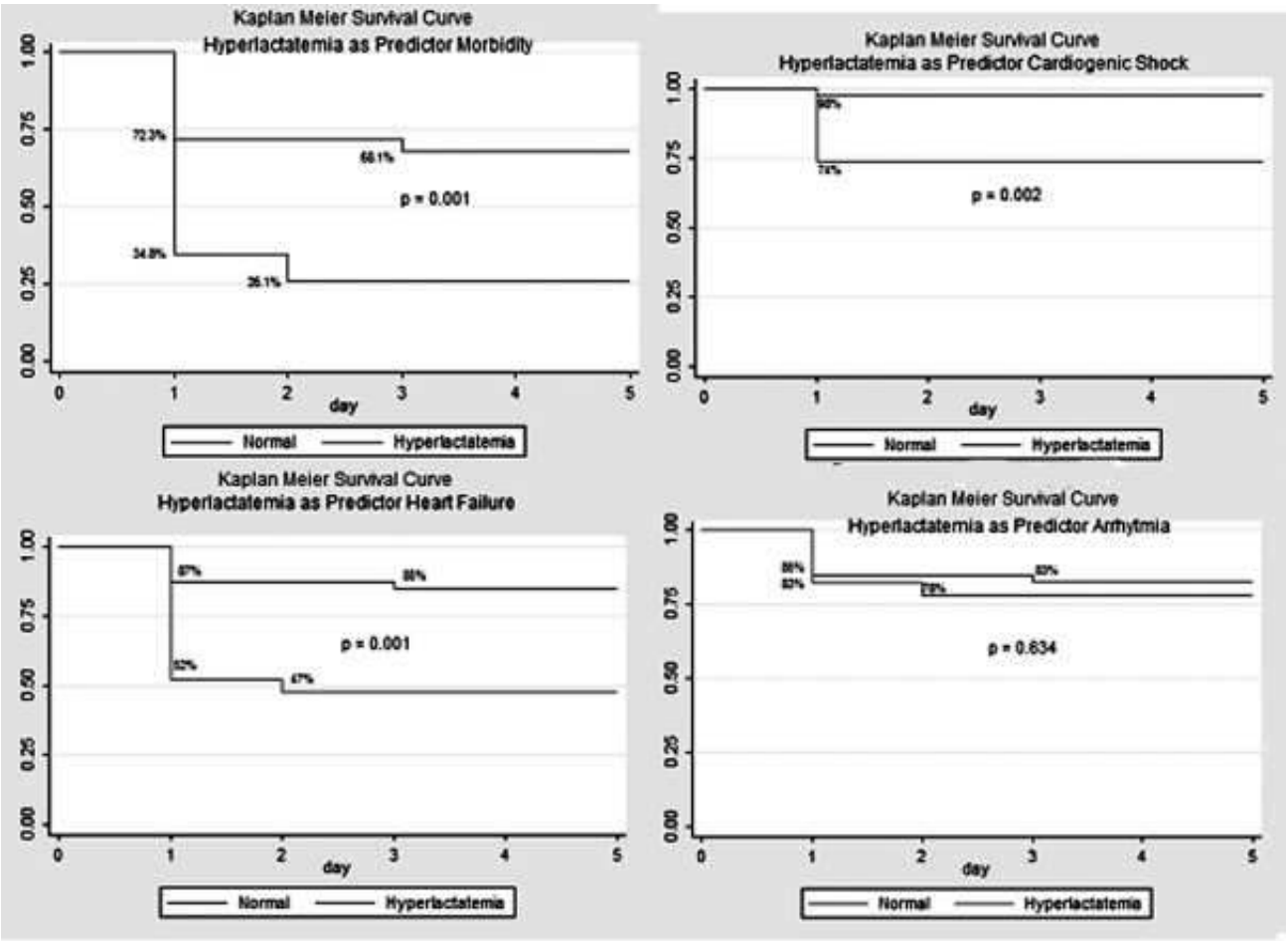

Figure 2. The Kaplan Meier Curve displays hyperlactatemia as predictor morbidity (P=0.001) , cardiogenic shock (P=0.002), and heart failure (P=0.001). There was difference outcome arrhythmia between two group but not statistically significant (P=0.634).

Table 2. Multivariate relations of clinical characteristics to morbidity

Variabel	HR	95 % CI	P
Hiperlaktatemia	2.616	1.159 to 5.906	0.021
Sex	0.724	0.209 to 2.508	0.610
Education	0.969	0.722 to 1.302	0.836
Dislipidemia	0.373	0.132 to 1.056	0.063
Diabetes Mellitus	1.816	0.494 to 6.673	0.369
Smoking	0.916	0.392 to 2.140	0.839
Diagnosis	1.143	0.508 to 2.569	0.747
CKMB	0.414	0.164 to 1.045	0.062
Random blood sugar	0.999	0.992 to 1.008	0.994

adrenaline level, or alcohol intake, are excluded from the population.[6,7]

There is no agreement about the optimal time interval between serial lactate sampling. Jansen et al.(cited from 6) aimed to reduce lactate by 20% per 2 hours, and managed to reduce mortality significantly in the intervention group. Therefore, based on the reviewed articles, examination lactate on admission,two, and 24 hours seems reasonable to be able to follow the trend.

This study shows 23 patients has hyperlactatemia and 47 patients without hyperlactatemia. This maybe caused by time required for lactate to increase. Lactate sensitivity would increase if patients less than 2 hours onset were excluded. Further investigation is required to determine whether pheriperal lactate concentration reflects myocardial lactate level.[3,4]

Two additional considerations are important when clinical myocardial ischemia is assessed by the amount of lactate production. Most clinical studies are based on sequential measurements in the same patient, e.g.,before and after treatment of a patient in cardiogenic shock. However, the natural time-course of the rate of lactate production during a constant degree of ischemia has not been defined; with constant hypoxemia in isolated heart preparations, the rate of lactate production progressively decreased over time. Thus, repeated measurements of myocardial lactate production in a patient with ischemic heart disease might be expected to change with time, despite a constant degree of myocardial ischemia. Second, myocardial lactate production in man is usually assessed by comparison of the coronary sinus and arterial concentrations. However, the coronary sinus level represents a mixed venous sample that results from the combined drainage from the ischemic and normally perfused regions of the ventricle. These limitations are generally recognized as possible sources of error in interpreting the pattern of myocardial lactate metabolism; however, the magnitude of the error that may result has not been quantified. Direct evaluation of these factors in man is obviously difficult, because it is virtually impossible to study the metabolic behavior of ischemic human myocardium over a range.[8,9]

Ischemia due to decreased coronary perfusion leads to muscle hypoxia and necrosis which compromises myocardial contractility. This leads to decreased cardiac output and a subsequent drop in the arterial blood pressure. Simultaneously,the body's sympathetic system responds to the reduced blood pressure by increasing vasoconstriction. The hormonal system is also activated leading to salt and water retention. This has a detrimental role, as the coronary perfusionis further compromised. A vicious cycle is thus created and it leads to decreased perfusion at the tissue level. Lacticacidosis and hypoxia eventually sets in, which further compromisethe myocar-dial contractility until the arterial blood pressure is not maintained to a level needed to sustain life.[9]

Cardiogenic shock caused by inadequate perfusion result in increased anaerob metabolism and lactate production. Inotrop and microvascular dearrangement also increased lactate. Hipoperfusion of kidney and splanchnic caused functional disturbance and make persistence lactic acidosis.[10,11]

Lazzeri[11] showed hyperlactatemia is independent predictor mortality only in patient class Killip III-IV [OR=1.17 (95% CI=1.05 to 1.30),P=0.003). The finding that hyperlactatemia is not predictor of arrhythmia in AMI patient may be reflection of difference patomechanism of arrhythmia. Post infarction arrhythmia mechanism involved ischemia region near infarction area. In arrhytmogenic area there were release of metabolit as potassium, calcium, cathecolamines, with low level of ATP inspite of hypoxemia. Arrhytmia also caused by fibrotic area of infarction.[11]

Disturbances of cardiac rhythm, which affect 90% of cardiac infarction patients caused by ischaemia, hypoxia, lactic acidosis, and abnormality hemodynamic. Beside that autonomic-nervous system imbalances, electrolyte abnormalities, alterations of impulse conduction pathways or conduction abnormalities, drug toxicity can provoke arrhythmia.[11]

Arrhytmia not merely caused by tissue hypoperfusion. Mechanism of arrhythmia is the presence of substrat of arrhythmia that involved ischemia zone, not in the infracted tissue. Zona of arrytmo-

genic released metabolit, potassium, calcium, and cathecolamine, with low ATP level and hypoxemia.[10,11]

CONCLUSION

Hyperlactatemia is an independent predictor of morbidity, cardiogenic shock, and heart failure in AMI patients. In the other hand, hyperlactatemia is not an independent predictor of arrhythmia in AMI patients.

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