EVALUATION OF A COMPREHENSIVE RISK FACTOR INDEX FOR ACUTE CORONARY INSUFFICIENCY

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ABSTRACT
Earlier risk assessment for acute coronary insufficiency has been done on the basis of "logistic function" and multiple regression analysis. Such an approach does not take into account the pathophysiological relationships amongst risk factors and individual medical data. An alternative approach based upon physiological modelling of myocardial oxygen demand and oxygen supply by the coronary circulation is presented. The ratio of the two is termed the adaptation ratio. Sensitivity of this ratio to parameter perturbation is the risk for that particular parameter. Sum of the sensitivities for the various risk factors gives the risk index. A clinical study on 40 subjects in the age group 35 to 60 is underway to assess the validity of the approach.

INTRODUCTION
Studies have identified major and minor risk factors associated with acute coronary insufficiency (ACI). Hypertension, smoking, obesity, inadequate exercise are some of the important factors. There are a host of other risk factors which seem to have variable correlation with the occurrence of ACI. Earlier studies analyzed the population data by methods such as multiple linear regression analysis and derived the correlation coefficient between the risk factors and the endpoint [1]. Although this approach helped to distinguish between major and minor risk factors it did not help significantly in categorising individuals into high and low risk groups. For this purpose the risk assessment concept was developed [2]. This term implies the process of quantifying the relationship between the probability occurrence of ACI and personal and environmental risk factors. A popular technique of arriving at the probability is to use a logistic function

\[ P(\text{disease}) = \frac{1}{1 + e^{a - b_1 x_1 - b_2 x_2}} \]

\[ P \] is the probability of the occurrence of ACI, \( x_1, \ldots, x_n \) are risk factors or individual characters, \( a \) is a constant and \( b_1, \ldots, b_n \) are coefficients which relate the risk factors to the overall risk. From the population data these coefficients have been derived by different statistical techniques. The method of Walter and Duncan [3] which does not entail an assumption regarding the distribution of the characteristics is commonly adopted. Risk probability of an individual can be obtained by substituting the magnitude of the characteristics of the subject in Eqn. 1. All these methods are statistical data matching procedures and do not go into the pathophysiological relationships amongst the characteristics and with the disease process. These associations are complex and in many cases not well understood. Even so, the time has come for taking a new direction of analysis based upon physiological relationships. No doubt a large part of the functional model will have to be described by somewhat arbitrarily selected functions. Still this formulation may give a risk index which reflects better the outcome when there are multiple marginally abnormal risk factors present.

MODEL
For risk index formulation the primary function of the coronary system may be considered to be the supply of oxygen to ventricular tissue. Oxygen requirement (D) depends upon the work load of the heart which may be approximated to the external work of the heart (W).

\[ W = K_1 p_s c \]

\[ C = \frac{P_c}{R} \]

Cardiac output exerts a negative feedback control over the heart rate. Mental stress and exercise level are also determinants. A quantification M for mental stress is assumed and the functional relation is selected such that the heart rate remains normal at zero stress and with increasing stress rises gradually. A similar pattern is adopted for exercise

\[ H = \frac{K_2 (1 + M_1/2)^{2/3} \cdot E + E_a}{\epsilon_3} \]

\[ W = \frac{K_3 p_s (1 + M_1/2)^{2/3} \cdot \epsilon_r \cdot E_a}{\epsilon_3} \]
Peripheral resistance increases with stress and release of catecholamines but decreases with exercise and so

$$R = (R_r + K_4 M_2)/E_a$$

leading finally to the work and with scaling to the oxygen demand as

$$D = K_5 P_d (1 + M_1/2)^{2/3}$$

Next supply of oxygen is to be considered. Vascular compression limits systolic flow and during this period any atherosclerotic narrowing will not be significant while during the diastolic period this factor is of importance. Vessel spasm too needs to be accounted for in the diastolic period. A vessel narrowing parameter \(V_n\) which is a function of spasm, high cholesterol and LDL levels as well as the time duration for which the abnormal levels have existed can be defined. Then applying Poiseuille's equation the coronary flow \((F_c)\) is

$$F_c = K_s P_d (r - K_s P_d)^* + K_{io} P_d (r - V_n)$$

The constants \(K_s\) and \(K_{io}\) incorporate the blood viscosity term and systolic/diastolic times. In the coronary system the oxygen extraction is high. Hence per unit of blood flow the oxygen delivery will depend upon the hemoglobin level \((H_b)\). A formulation reflecting reduction in oxygen delivery as the \(H_b\) falls below 15.4 g/dl can be included in the flow to give available oxygen \((O_a)\)

$$O_a = \frac{H_b}{30.8 - H_b} F_c$$

Under steady state conditions \(O_a\) is equal to \(D\) and an adaptation ratio \((A)\) can be defined as

$$A = \frac{Q_a}{D}$$

A perturbation in any parameters in the system will change \(A\). Parametric sensitivity may be taken as an estimate of the risk of that parameter. For instance the risk associated with systolic pressure rise will be the partial differential of \(A\) with respect to \(P_s\). The risk index \((RI)\) becomes the sum of the sensitivities of the parameters.

$$RI = \frac{\partial A}{\partial P_s} + M + \frac{\partial A}{\partial V_n}$$

Special features of this model are that
- Risk index as well as the contribution to the risk of a particular parameter depends upon the values of other parameters of that particular individual. For the same perturbation risk will differ from individual to individual. This fact is borne out by common medical observation
- In time for a subject the parameter magnitudes will change and a new equilibrium state is established. The risk associated with each factor will also change. Clinical finding supports this pattern. For instance a certain magnitude of \(P_s\) rise in the young carries greater risk than in the elderly.
- By means of various measurements the appropriate values of the constants may be arrived at. These will change for an individual in course of time.
- Certain functional relationships have been assumed but the approach is generalized. On the basis of detailed pathophysiological studies better relations may be arrived at and used in the model. Additional parameters for instance ECG abnormalities and smoking habit may also be included if the relationship with cardiac function in terms of oxygen supply and demand can be established. Available population data and risk estimates by the conventional method can help in this respect.

CLINICAL STUDIES

A clinical study is underway on a group of 40 persons in the age group 35 to 60 years with no previous history of ACI. Complete physical examination with quantification relevant to the model are carried out. Laboratory investigations include blood chemistry, hematology and urine examination. Cardiac output at rest and during exercise is determined by impedance plethysmography. All the data provides information to arrive at the relations and constants. Since the study has been only over the past one and a half year it is too early to comment on the validity of the model. But of the two subjects, both non smokers and with no ECG abnormality, identified as at high risk, one had an episode of MI.

REFERENCES


K1-K10 : Constants; \(P_s\): Average systolic pressure; \(P_d\): Average diastolic pressure; \(C\): Cardiac output; \(R\): Peripheral resistance; \(R_r\): Resting peripheral resistance; \(H\): Heart rate; \(E_{a}\): Average exercise level; \(E\): Exercise excess over the average; \(r\): Average coronary vessel radius when no atherosclerotic narrowing present.