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An attempt to describe heart attacks via continuum damage mechanics

Dedicated to Professor Zenon Mróz
on the occasion of his 70^{th} birthday

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IN AN EARLIER PAPER the author expressed the evolution equations of classical continuum damage mechanics in terms of unit dissipated power and proposed an extension to biological materials *in vivo*, adding a term describing the recovery. In the present paper an analogy with evolution of the coronary artery disease is established. If we denote by S (relative stenosis) one minus the ratio of current luminal area to the initial area, then the condition $S = 1$ at a certain point of the artery means complete blockage at this point resulting in a heart attack (myocardial infarction). This corresponds to the condition of critical state $D = 1$ in damage mechanics, where D denotes a scalar measure of damage. Making use of this analogy, an evolution equation for S is proposed, with unit dissipated power replaced by unit power of flow in individual cross-sections of coronary arteries and, subsequently, by the heart power. Further, another evolution equation describes the required heart power in terms of external loadings acting on the organism as a whole. Numerical integration of the evolution equations proposed makes it possible to distinguish the loadings leading to a myocardial infarction from those subject to recovery. Also, the description of stable and unstable angina pectoris is discussed and illustrated by numerical examples.

Notations

A	current luminal area of an artery
A_0	initial (reference) luminal area of an artery
ΔA	elementary area carrying the stress σ
C_{d}	modulus of resistance of the material to damage
C_{r}	modulus of recovery of the material
D	damage parameter of the material
D_0	initial damage at the moment of loading
G_{d}	modulus of resistance of coronary arteries to heart loading
G_{r}	modulus of recovery of coronary arteries
N	power of heart
N_{f}	power of flow in a current cross-section s of the artery
S	measure of heart damage (relative stenosis)

S_0	initial heart damage (due to atherosclerosis)
X	coordinates of a point in the body
Ψ	unit dissipated power at a current point X of the body
g	dimensionless modulus combining G_{d} and G_{r}
h	dimensionless power of heart
k_i	concentration of ith catecholamine in blood
m_j	mass of the drug j taken at $\tau = \tau_o$
n_H	heart rate, frequency of heart contractions,
p	pressure in coronary arteries
$\bar{p}$	heart pressure as a function of current volume of the ventricle
s	coordinate along the arc of axis of an artery
t	time
v	velocity of flow
z	dimensionless power of external loadings
σ	uniaxial mechanical stress in a material
τ	dimensionless time
φ	coefficient of nonlinearity of recovery in a biological material
ψ	coefficient of nonlinearity of recovery of coronary arteries

1. Introduction

CARDIOVASCULAR BIOMECHANICS is a well developed discipline, in particular the analysis of blood circulation, heart valve prostheses, strength and deformability of myocardium, CHANDRAN [4]. The present treatment is quite different: the mathematical model of coronary artery disease is based on a phenomenological approach requiring a relatively small number of parameters. Blood circulation itself is not analysed, just the conditions of flow in coronary arteries, in other words – the decrease of current luminal area of these arteries. The paper formulates and applies an analogy between the description of critical state of a structural element by continuum damage mechanics generalized to biological materials, and the description of heart attacks. In what follows, we identify the popularly used term "heart attack" with "acute myocardial infarction" (AMI) and consistently use the latter term throughout the paper. Evolution equations for individual parameters are proposed.

This study of necessity addresses the purely deterministic aspects of myocardial infarction, treating the coronary arteries as tubes with lumina narrowed by atheroma with superposed vasoconstriction. By definition, this is a simplification of the *in vivo* process where events such as plaque fissuring and thrombus formation are responsible for the actual myocardial infarct, and secondary events such as heart failure and arrhythmias may lead to death. This simplification is necessary in order to clarify the initial model, but there is clearly scope for expanding the model by including probabilistic considerations.

Continuum damage mechanics, in its simplest scalar form, is based on the following evolution equation for damage parameter during the creep process in a

structural element, proposed by KACHANOV [18]:

$$\frac{dD}{dt} = \frac{1}{C_1}\left(\frac{\sigma}{1-D}\right)^q . \tag{1.1}$$

The local damage parameter $D = D(X,t)$ is here defined by the formula

$$D = 1 - \frac{\Delta A}{\Delta A_0} . \tag{1.2}$$

X denotes the coordinates of the point under consideration, t – time, ΔA_0 – the elementary initial cross-section transmitting the mechanical stress $\sigma = \sigma(X,t)$, ΔA – the elementary section decreased in view of microdamage (carrying section), C_1 and q are material constants.

Equation (1.1) formed the basis for a widely developed branch of mechanics, called since late seventies the "continuum damage mechanics". We mention here just the monographs by KACHANOV [19], LEMAITRE [21], KRAJCINOVIC [20], SKRZYPEK and GANCZARSKI [31].

The local condition $D = 1$ reflects the decrease of the elementary carrying cross-section ΔA at the point X under consideration to zero and formation of a certain critical state, namely initiation of a macrocrack. In the case of a homogeneous state of stress, this is equivalent to a total collapse of the structural element, whereas in the case of non-homogeneous states of stress the global condition (reached at a certain time $t = t^*$)

$$\sup_{x \in V} D = 1, \tag{1.3}$$

where the symbol sup denotes upper bound of the function in the domain under consideration; it is also often used as that determining a limit of safe work of the element with the volume V. The location of the point $X = X^*$, where the supremum of D is reached (dangerous point), may be of essential importance. If this is a crucial point, then the structure shows immediate collapse; on the other hand, if X^* is less important, then the condition (1.3) results just in an initiation of a macrocrack leading to total collapse after a certain time. Consider, for example, two simple four-bar trusses shown in Fig. 1, a and b. Thicknesses of the lines correspond here to the cross-sectional area of individual bars. In case (a), first the lower bar will collapse; it carries the whole force P and hence this critical state is equivalent to collapse of the truss as a whole. In case (b), first the vertical upper bar will collapse, but even without that bar the three-bar truss will remain a load-carrying structure. If the upper bound of D is reached simultaneously in several points X_i^*, then the most crucial point is decisive.

Recently, ŻYCZKOWSKI [38] expressed the evolution equations of continuum creep damage mechanics in terms of unit dissipated power Ψ and proposed an

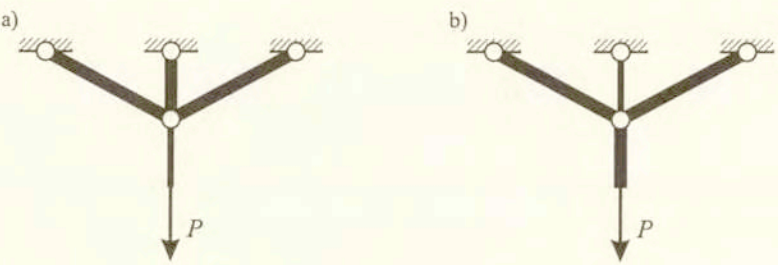

FIG. 1. Basic interpretation: two four-bar truss systems with various cross-sections of individual bars. Secondary interpretation: two schemes of coronary arteries with various luminal area of individual arteries.

extension to biological materials *in vivo*, namely a term describing recovery (or related phenomena, called healing, repair, regeneration, restoration, maintenance) was added. The relevant equation has the form

$$\frac{dD}{dt} = \frac{1}{C_{\mathrm{d}}}\sqrt{\frac{\Psi}{1-D}} - C_{\mathrm{r}}\left[(D-D_0) - \frac{\varphi}{1-D_0}(D-D_0)^2\right], \tag{1.4}$$

where C_{d} denotes the modulus of resistance of the material to damage, C_{r} – the modulus of recovery (with the dimension of reciprocal time), whereas φ – dimensionless coefficient of nonlinearity of recovery; practically $0 \leq \varphi \leq 1$. Moreover, D_0 denotes the initial value of damage, before application of loading; in structural materials it may be due to oxydation (corrosion), in the case of growing tree – to rot, and in the case of a bone – to osteoporosis. Equation (1.4), proposed for biological materials *in vivo*, should be regarded just as an initial step in this direction. First, the variety of such materials may require individual approach in every case, or, at least, for particular classes of biological materials. Second, regeneration or recovery of such materials may consist of several biological processes like growth (mass change), remodelling (property change) and morphogenesis (shape change) in adaptive form, TABER [34], and any of those processes may require a separate description.

The revelant literature was discussed in [38]; here we add just some more recent related references by COWIN [6] (survey on description of internal and surface remodelling), FRANCFORT and MARIGO [10] (damage evolution equations describing osteoporosis), DOLIŃSKI [9] (damage evolution in fatigue processes of bone cement specimens), JEMIOŁO and TELEGA [16] (bone remodelling combined with homogenization). However, most of these approaches, sometimes rather complicated, do not allow for recovery. In the present paper we use the very simple approach (1.4) but with recovery taken into account.

The aim of the present paper is to point out an analogy between the evolution of creep damage in biological materials and the evolution of damage in human

coronary arteries, and to use this analogy to a phenomenological description of coronary artery disease and myocardial infarction.

2. Analogy with the development of coronary artery disease and occurrence of myocardial infarction

Now we show an analogy between creep damage and rupture of biological materials on one side, and heart damage and myocardial infarction on the other. There exist, of course, various forms of heart damage. Here we consider just one, but probably the most important form of heart damage, namely the coronary artery disease being the direct cause of most myocardial infarctions. Coronary artery disease depends, first of all, on narrowing (stenosis) of the luminal cross-section of coronary arteries resulting in reduced supply of blood and oxygen to the heart muscle. Narrowing of the lumen is usually due to atherosclerosis and to coronary vasoconstriction. Atherosclerosis is characterized by slow increase of thickness of walls of coronary arteries up to formation of atheromatous plaques; it depends on many risk factors, specified below, but is almost independent of external loadings. On the other hand, coronary vasoconstriction develops relatively quickly and depends essentially on external loadings of the human organism, also specified below.

The measure of heart damage under consideration will be defined as relative stenosis of coronary arteries S, namely, in full analogy to Eq. (1.2),

$$S = 1 - \frac{A}{A_0}, \tag{2.1}$$

where $A(s,t)$ denotes current effective luminal area of an artery, $A_0(s)$ – reference luminal area (without damage). These quantities are functions of position of the point along the arc of axis of the artery s, moreover A depends on time. As the luminal area A we understand the cross-section after narrowing resulting from all possible reasons, in particular atherosclerosis and vasoconstriction, but also from a thrombosis or fissuring of an atheromatous plaque. The area A may also depend on the blood pressure p, but this dependence will not be taken into account.

The condition (reached at a certain time $t = t^*$)

$$\sup_{s \in CA} S = 1, \tag{2.2}$$

where CA denotes the set of all coronary arteries, results in complete blockage of blood flow in a certain coronary artery and so it may be regarded as the condition of occurrence of acute myocardial infarction, FROELICHER and ATWOOD [11], PASTERNAK *et al.* [27]. The point $s = s^*$ where the supremum of S is reached (dangerous point), is very important here, similarly, as in the case of creep damage

of a structural element. If the point s^* appears at a major coronary artery, in particular in the left circulation, then the myocardial infarction is more likely to result in the death of the patient, whereas if it appears at a marginal artery, after subdividing into smaller branches, then the chances of survival are much greater. Consider now Fig. 1 as the sketch of a system of coronary arteries and suppose that a ventricle is located in the upper side of both figures (a) and (b), blood flows in opposite direction to that shown by the arrows, and thicknesses of lines reflect current luminal area of individual arteries at the instant t_1. This luminal area is subject to decrease. In case (a) we may expect blockage of the major coronary artery probably leading to death of the patient, whereas in case (b) rather the central artery after branching will be blocked, resulting in a less dangerous myocardial infarction. The case of several points $s = s_i^*$ corresponds to that described in Sec. 1.

In view of the analogy between the measure of material damage D and of coronary artery damage S shown above, and the analogy of critical states described by Eqs. (1.3) and (2.2), we postulate for S an evolution equation in a form analogical to Eq. (1.4). Instead of the unit dissipated power Ψ in Eq. (1.4), we substitute here the unit power of blood flow in coronary arteries. Power of a flow, RICHTER [28], is given by

$$N_{\mathrm{f}} = Apv \tag{2.3}$$

where p denotes pressure, and v – velocity of the flow; as the unit power ν_{f} we understand this power divided by the luminal area,

$$\nu_{\mathrm{f}} = \frac{N_{\mathrm{f}}}{A} = pv. \tag{2.4}$$

It is assumed that $\nu_{\mathrm{f}} = \nu_{\mathrm{f}}(s,t)$ at any point s is proportional to the actual heart power (work per minute) $N = N(t)$ and, in analogy with Eq. (1.4), we propose the following hypothesis for the development of heart damage (evolution equation for stenosis S):

$$\frac{dS}{dt} = \frac{1}{G_{\mathrm{d}}}\sqrt{\frac{N}{1-S}} - G_{\mathrm{r}}\left[(S-S_0) - \frac{\psi}{1-S_0}(S-S_0)^2\right] \tag{2.5}$$

where G_{d} denotes the modulus of resistance of coronary arteries to the heart power, G_{r} – the modulus of recovery of coronary arteries, connected here with an increase of luminal area of these arteries (e.g. as a result of decrease of vasoconstriction or thrombus destruction), ψ – coefficient of nonlinearity of this recovery. The moduli G_{d} and G_{r} may depend here on the spatial variable s and on time t; a certain discussion of the latter dependence will be given in Sec. 8, where the effect of drugs will be considered. Moreover, these moduli may depend

on composite structure of the artery wall and on residual strains in it; the problem of residual strains was discussed e.g. by GREENWALD *et al.* [14].

The function $S_0 = S_0(s)$ in Eq. (2.5) denotes the initial damage of coronary arteries, namely damage at the instant of application of a certain, currently considered external loading $t = 0$; the value of S_0 is, first of all, due to atherosclerosis. Atherosclerosis is defined as formation of fatty streak and of fibrous plaques that cause stenosis and in the case of coronary arteries, reduce the blood supply to the myocardium. It may be regarded as the end result of various causes from among the broader group of risk factors, like hypercholesterolaemia, hypertension, clinical diabetes, excessive smoking and obesity, ROSS [29]. It also changes in time and should be described by a separate evolution equation; however, the changes of S_0 are very slow and without going into details, we simply assume that the function $S_0 = S_0(s)$ is known and we assume $S = S_0$ for $t = 0$ as the initial condition for Eq. (2.5).

The evolution equation proposed above, (2.5), will be interpreted as describing the effects of vasoconstriction, essentially dependent on loadings, specified in the next section. Muscular elastic arc of coronary vessel wall provides a mechanism whereby normal (vasoconstriction) or abnormally intense (vasospasm) increases in vasomotor tone may affect the lumen, RUTHERFORD and BRAUNWALD [30]. Vasoconstriction and vasospasm may cause intimal damage that can initiate formation of an atherosclerotic plaque, GERTZ *et al.* [13], PASTERNAK *et al.* [27], they may precipitate coronary thrombosis, VINCENT *et al.* [36], they expose the myocardium to transient ischemia, angina pectoris, or even result in sudden cardiac death, MASERI *et al.* [24], MYERBURG and CASTELLANOS [26]. Description proposed here is deterministic, hence it cannot reflect such phenomena as myocardial infarction resulting from fissuring of an atheromatous plaque and/or thrombus formation. Though the criterion of a myocardial infarction (2.2) is then also satisfied, a proper mathematical description of that phenomenon would require an evolution equation in probabilistic approach.

The power of heart N, as of a pumping system, depends on the heart rate (frequency of heartbeat, pulse) n_H, on the stroke volume V_S equal (for each ventricle) to the difference between end-diastolic volume and end-systolic volume, and on the change of pressure $\bar{p}$ in the course of pumping. It may be described by the formula (in the case of stationary motion)

$$N = -n_H \left[\int_{LV} \bar{p} dV + \int_{RV} \bar{p} dV \right] = \eta n_H \left[(p_{\text{sys}} V_S)_{LV} + (p_{\text{sys}} V_S)_{RV} \right], \tag{2.6}$$

where the line integrals are taken around the pressure-volume loops for the left ventricle (LV) and right ventricle (RV), respectively, p_{sys} denotes the maximal

(end-systolic) pressure in each ventricle, whereas the coefficient $\eta \leq 1$ depends on the variation of pressure $\bar{p}$ during the process and is simply defined by the second part of Eq. (2.6). In the case of non-stationary motions, the derivative of the square bracket with respect to time should be taken.

The term "power", namely the power of external loadings of the human organism and the power of heart, is used in cardiology in parallel with the term "workload": BRAUNWALD *et al.* [3] define stroke power (heart power) as the rate of performance of stroke work, whereas GROSSMAN [15] uses the term "workload" as the power of external loadings. Here we employ consistently the term "power", as used in physics and engineering, but in a slightly extended meaning, since psychological loadings (emotional stresses, defined in Sec. 3) will also be considered.

Many authors, e.g. GROSSMAN [15], and DENNIS [8], join the power of heart directly with the power of external loadings (often the power demanded by external agencies), using in parallel the classical units kgm/min and the units of the metabolic equivalent system (METS). A MET is defined there as a unit of workload that approximates consumption of 3.5 ml 0_2/kg min, the amount of oxygen required under basal conditions. A level of 2 METS corresponds to doubling of the 0_2 consumption and – according to the authors – is equivalent approximately to 75 kgm/min.

However, such an approach is not general enough: it may be used just for stationary states (both powers being constant in a longer period of time), whereas for short-term intensive external loadings, like weight-lifting, it cannot hold: the power of external loadings drops suddenly to zero, but the oxygen consumption remains high for a longer time. Also myocardial infarctions often take place with a considerable delay after external loadings are relieved, PASTERNAK *et al.* [27], hence it should be stated that the heart power depends on the power of external loadings of human organism not directly, but via a differential evolution equation. Now we are going to propose such an equation with at least partial explanation of the mechanism of that evolution.

3. Evolution equations for heart power

The heart should supply blood and oxygen to individual cells to meet the metabolic demand depending in an essential manner on external loadings of the organism.

External loadings may be divided into two groups: physical loadings and psychological loadings, called also emotional stresses (not to be confused with mechanical stresses used in the introduction to the present paper). Coronary vasoconstriction has been observed during exercise, RUTHERFORD and

BRAUNWALD [30], and many recent studies confirmed the importance of physical activity and pointed to emotional stress as another important trigger of myocardial infarction, JENKINS [17], TOFLER *et al.* [35], PASTERNAK *et al.* [27]. The importance of the "rate of work" or "hurrying" (it means of the power, and not of the loading itself) is stressed e.g. by RUTHERFORD and BRAUNWALD [30].

Defining physical loadings is just apparently simple: the relevant power N_p might be defined as a scalar product of force and velocity (e.g. weight of a body times its lifting velocity). As a matter of fact, there exist also many other physical loadings of the organism, not conforming directly to the above definition, for example marching along a horizontal way, in particular with a weight. This problem was considered, for example, by MILLER and VERSTRAETE [25], GARCIA *et al.* [12]. Such types of physical loadings should be suitably estimated and added. So, we assume that N_p reflects the power of all physical external loadings with appropriate overcalculations.

The effect of N_p on heart power is very diverse; to simplify the problem, we consider just one factor transmitting the power and subsequently resulting in heart damage, namely endocrine secrection of catecholamines and their circulation in blood vessels, COUSINEAU *et al.* [5]. Excessive secretion of catecholamines, in particular if alpha adrenoceptors are dominating, produces vasoconstriction and vasospasm, CREA *et al.* [7], BRAUNWALD *et al.* [3], which can lead to myocardial infarction, BERTEL *et al.* [1], PASTERNAK *et al.* [27]. Each of the most important three catecholamines, namely epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine, may be governed by a separate evolution equation

$$\frac{dk_i}{dt} = f_i(N_p, k_i) \quad i = 1, 2, 3, \tag{3.1}$$

where k_i denotes concentration of ith catecholamine in blood. In view of further simplification we consider just one kind of catecholamines and assume that the rate of concentration of this kind k is proportional to N_p.

Definition of psychological loadings, called also emotional stresses, is much more difficult, and an objective definition seems rather impossible, since the same cause can bring for one organism great stress, and for the other – none. Hence we assume here just a subjective definition of power of external psychological loadings N_s via its effects for the organism under consideration, and namely via the relevant rate of concentration of catecholamines in blood. So, for both loading types, the rate of concentration of catecholamines amounts to

$$\frac{dk}{dt} = \frac{N_p}{c_1} + \frac{N_s}{c_2}, \tag{3.2}$$

where c_1 and c_2 are the relevant coefficients of proportionality. The evolution

equation should also allow for elimination (decomposition and excretion) of catecholamines; finally, we determine the concentration of catecholamines in the cardiovascular system by the evolution equation

$$\frac{dk}{dt} = \bar{N} - c_3(k - k_0)\,, \tag{3.3}$$

where $\bar{N}$ denotes briefly $(N_p/c_1)+(N_s/c_2)$, the second term allows for elimination of the catecholamines, c_3 is the coefficient of the rate of elimination, and k_0 — concentration of the catecholamines corresponding to work of the heart at zero external loadings (it means at rest and without emotional stresses). For the sake of simplicity, the term describing elimination of the catecholamines was assumed here in a linear form; introduction of nonlinearity like in (1.4) and (2.5) is also possible.

The presence of catecholamines results in an increased demand of heart for oxygen and hence it results in an increase of the required heart power N_e. The dependence $N_e = N_e(k)$ may be represented by a Taylor series; leaving in this series for simplicity just two terms, we may write

$$N_e = N_o + \left(\frac{dN_e}{dk}\right)_0 (k - k_0)\,, \tag{3.4}$$

where N_0 is the required heart power corresponding to concentration of catecholamines at rest and without stress, whereas the derivative $(dN_e/dk)_0$ is a certain constant expressing the effect of concentration of catecholamines on the required heart power. This effect is realized mainly by increase of the heart rate n_H, but also of the pressure p_{sys}.

If there are no losses in the cardiac system, then the required power is equal to the real heart power (2.6), and may be substituted into the evolution equation (2.5). If there are losses, e.g. due to leakage of valves (regurgitation), then a suitable coefficient of tightness μ ($\mu \leq 1$), should be introduced, and the real heart power N which ensures the required heart power N_e is given by

$$N = \frac{N_e}{\mu}\,. \tag{3.5}$$

This enlarged value should be substituted into the evolution equation (2.5).

Equations (3.2), (3.3) and (3.4), express the heart power N in terms of powers of the external loadings N_p and N_s via the parameter of concentration of catecholamines k; elimination of k will be given below in dimensionless form.

4. The evolution equations in dimensionless form

Before going to a more detailed analysis of the evolution equations, first we present them in a dimensionless form, thus reducing the number of parameters.

The moduli G_d and G_r in Eq. (2.5) may be functions of time in a double manner. First, they may be subject to a relatively quick change e.g. as a result of application of appropriate drugs; second, they change slowly (usually decrease) with the age of the patient. The latter problem was discussed by WEISFELDT *et al.* [37]; they noticed the age-related diminished catecholamine responsiveness. When considering Eq. (2.5), where the time is measured in hours and minutes, the second change is not particularly important, but the first one should be allowed for. So, we introduce the dimensionless time τ by a differential formula

$$d\tau = G_r(t)dt\,. \tag{4.1}$$

Further, we denote the product of the moduli $G_d G_r$ by G and allow for its dependency on time by the formula $G = G_0 g(\tau)$, where G_0 is a reference value, for example without taking drugs; the dimensionless function $g(\tau)$ will be discussed in detail in Sec. 8. Finally, dividing both sides of Eq. (2.5) by G_r and introducing dimensionless heart power h by the formula $h = N/G_0^2$, we can eliminate all dimensional quantities and write

$$\frac{dS}{d\tau} = \frac{1}{g(\tau)}\sqrt{\frac{h}{1-S}} - \left[(S - S_0) - \frac{\psi}{1-S_0}(S-S_0)^2\right]. \tag{4.2}$$

Since ψ may be regarded as constant for the given organism (it changes slowly in a longer time interval), hence the process of damage evolution is here depending just on one dimensionless parameter h.

In order to estimate the values of the dimensionless time τ, introduced by Eq. (4.1), we integrate Eq. (4.2) in the simplest, rather abstract case of fully unloaded heart and linear recovery $h = \psi = 0$. Then the integral is of the form

$$S - S_0 = [S(0) - S_0]e^{-\tau}\,, \tag{4.3}$$

where $S(0)$ denotes the value of damage at the beginning of the recovery process under consideration. After the passage of time $\tau = 1$, the excess of damage over S_0 would decrease to $1/e$, it means to 0.367 of the initial value. This is a rather large reduction; one may assume that for individual organisms $\tau = 1$ corresponds to t equal to several hours.

Equations (3.3), (3.4) and (3.5) can be reduced to dimensionless form in the same manner. Differentiating equation (3.4) with respect to time we first obtain,

with Eq. (3.5) taken into account,

$$\frac{dk}{dt} = \frac{\mu}{\left(\frac{dN_e}{dk}\right)_0} \frac{dN}{dt}. \tag{4.4}$$

Comparing Eqs. (4.4), (3.3) and (3.4) we arrive at the equation

$$\mu \frac{dN}{dt} = \left(\frac{dN_e}{dk}\right)_0 \bar{N} - c_3(\mu N - N_0). \tag{4.5}$$

Now, introducing dimensionless time τ by Eq. (4.1), dimensionless heart powers h and h_0 as above, finally, defining dimensionless power of external loadings z and dimensionless ratio of the moduli of recovery λ by the formulae

$$z = \frac{1}{G_r G_0^2} \left(\frac{dN_e}{dk}\right)_0 \bar{N}, \qquad \lambda = \frac{c_3}{G_r}, \tag{4.6}$$

we rewrite Eq. (4.5) in the dimensionless form as follows:

$$\frac{dh}{d\tau} = \frac{z}{\mu} - \lambda\left(h - \frac{h_0}{\mu}\right). \tag{4.7}$$

The initial condition for this equation may be assumed in the form

$$h = \frac{h_0}{\mu} \qquad \text{for} \qquad \tau = 0, \tag{4.8}$$

which corresponds to the state of equilibrium before application of the loading with the power $z = z(\tau)$.

The last term in (4.7) may be interpreted as a self-protection mechanism to raise blood flow in the heart when needed. We repeat here once more that derivation of (4.7) via the secretion and excretion of catecholamines should be regarded just as an example; however, it is assumed that other mechanisms of power transmission result in similar evolution equations.

5. Stationary states

In contradistinction to the classical equation of continuum damage mechanics (1.1) which allows for a stationary state $dD/dt = 0$ just at vanishing loadings, $\sigma = 0$, the proposed evolution equations of heart damage (4.2) and of heart power (4.7) describe also the stationary or quasi-stationary states corresponding

to loadings different from zero. Assuming $dS/d\tau = 0$ and $dh/d\tau = 0$, we obtain from Eqs. (4.2) and (4.7) the following algebraic equations:

$$h = (1 - S)\left[(S - S_0) - \frac{\psi}{1 - S_0}(S - S_0)^2\right]^2 g^2(\tau), \tag{5.1}$$

$$\frac{z}{\mu} = \lambda\left(h - \frac{h_0}{\mu}\right). \tag{5.2}$$

The second of these equations determines the heart power in stationary state, corresponding to the constant power of external loadings z, or in quasi-stationary state in the case of slightly changing functions $z = z(\tau)$, $g = g(\tau)$, $\lambda = \lambda(\tau)$. It has always one root h, namely

$$h = \frac{z + \lambda h_0}{\lambda\mu}. \tag{5.3}$$

Just in this stationary case the heart power is linearly related to the power of external loadings and the latter may be expressed in METS with a reasonable level of approximation.

Then, if h is determined, Eq. (5.1) may be regarded as a nonlinear algebraic equation for the unknown S – measure of heart damage in stationary state or in quasi-stationary state in the case of slightly changing function $g = g(\tau)$. Depending on the values h and $g(\tau)$ this equation may have inside the interval $S_0 \leq S \leq 1$ two real roots, or one double root, or no real roots at all. If $h = 0$, then Eq. (5.1) has two roots: $S = S_1^* = S_0$ and $S = S_2^* = 1$; the first corresponds to coronary arteries damaged just as a result of atherosclerosis, whereas the second – to total damage (myocardial infarction). With an increase of heart power h we at first obtain two roots, one of which is located at the branch starting from $S = S_0$, and the other — at the branch starting from $S = 1$. The first root corresponds to a stable process, since an increase of h is connected with the relevant increase of $S = S_1^*$, whereas the second root corresponds to an unstable process, since a further increase of $S = S_2^*$ corresponds here to a decrease of h. The boundary value (double root) $S_1^* = S_2^* = S_{cr}$ corresponds to a maximum of the function $h = h(S)$ determined by Eq. (5.1). Equating the derivative dh/dS to zero we obtain the quadratic equation

$$5\psi S^2 - [3(1 - S_0) + \psi(4 + 6S_0)]S + [(2 - S_0 - S_0^2) + \psi(4S_0 + S_0^2)] = 0. \tag{5.4}$$

It is seen that the coefficient of S is always negative, hence the root of Eq. (5.4) located inside the interval $S_0 \leq S \leq 1$ may be written in the form

$$S = S_{\mathrm{cr}} = \frac{-b - \sqrt{\Delta}}{2a}, \tag{5.5}$$

where $\Delta = b^2 - 4ac$ is the discriminant of the quadratic equation (5.4), and a, b, c are the coefficients in this equation. The relevant maximal value of the heart power h for the stationary state $h = h_{\max}$ is given by Eq. (5.1) with substituted $S = S_{\mathrm{cr}}$ determined by formula (5.5).

The value S_{cr} separating stable and unstable stationary processes may be regarded as the point of critical stenosis, LEVIN and GARDINER [22], hence the notation S_{cr}. Usually it is assumed that the value of S_{cr} is close to 0.7, LILLY [23]. For $S > S_{\mathrm{cr}}$ the coronary blood flow is heavily reduced and individual cells of the heart muscle may be subject to damage. Detailed discussion is given below.

6. On experimental evaluation of parameters in the evolution equations proposed

The evolution equations proposed, even those presented in dimensionless form (4.2) and (4.7), require $1 + 3$ parameters to be determined experimentally, namely ψ, and μ, λ, h_0. In fact, the number of parameters is even larger, since measurements must be carried out in physical time, and not in dimensionless time. Moreover, we have to know the initial relative stenosis $S_0 = S_0(s)$, before vasoconstriction; it may be determined directly by coronary angiography methods.

Hence, two series of experiments are needed. Both series are difficult, but that concerning Eq. (4.7) seems to be easier. It needs several measurements of the heart power under external loading and at rest, for example in the course of weight-lifting and after weight-lifting. In the simplest case we could measure the oxygen consumption per unit of time and suppose that the heart power is proportional to that consumption. The effects of oxygen consumption on various aspects of the heart function were studied in a series of papers by SUGA *et al.* [32, 33], but the proportionality was found to be approximate and essentially depending on hemodynamic conditions. So, rather the integrals in formula (2.6) should be measured and their derivative with respect to time evaluated numerically.

Much greater experimental difficulties brings the evaluation of parameters in Eq. (4.2). One needs to perform subsequent measurements of coronary artery stenosis under external loading and during relaxation time. At present, coronary angiography does not allow for such measurements. Greater chances are given by scintigraphy and positron-emission tomography, but even these need further development.

In view of lack of any experimental verification of the equations proposed, some numerical examples will be given just for representative values of the parameters. Calculations for many sets of parameters were performed; we quote here just the results for the parameters being in agreement with known results

of other investigations (e.g. for critical stenosis point, mentioned above). We assume that the calculations refer to the dangerous point $s = s^*$.

7. Numerical examples, description of angina pectoris

For example, if $\psi = 0.3$, $S_0 = 0.3$, $g(\tau) \equiv 1$, then $S_{cr} = 0.726$, $h_{max} = 0.0332$; if $\psi = 0.7$, $S_0 = 0.5$, $g(\tau) \equiv 1$, then $S_{cr} = 0.745$, $h_{max} = 0.0066$. The first example refers to a heart in better health, with smaller atherosclerosis of coronary arteries ($S_0 = 0.3$) and larger resistance to the effects of damage ($\psi = 0.3$), whereas the second example – to a heart with larger atherosclerosis ($S_0 = 0.5$) and smaller resistance to the effects of damage ($\psi = 0.7$). Hence in the first case h_{max} is much larger than in the second, whereas in both cases the boundary values S_{cr} are almost equal to each other and close to the typical value of the point of critical stenosis given above. Diagrams of the function $h = h(S)$ for both sets of numerical data under discussion are shown in Fig. 2.

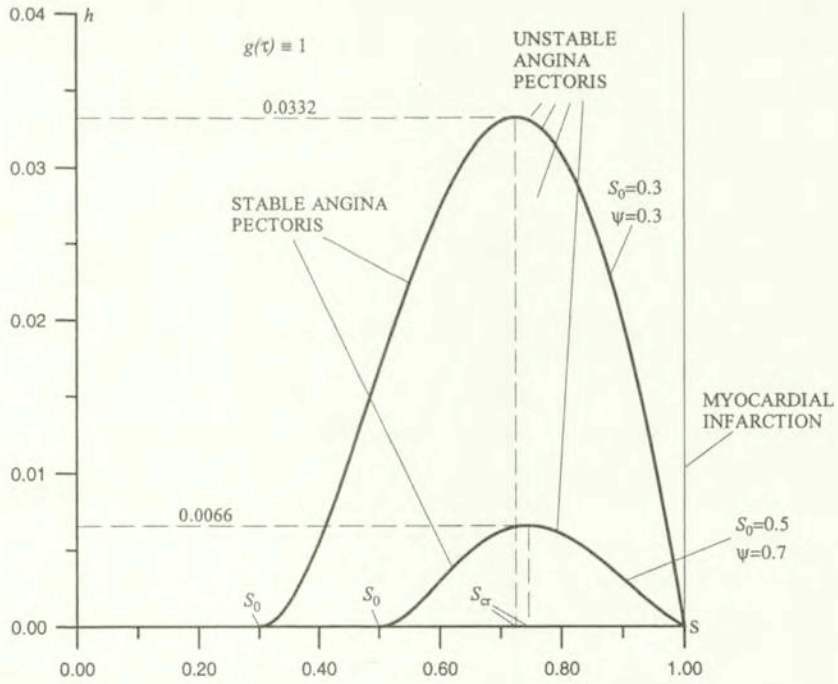

FIG. 2. Real heart power h in terms of heart damage S in quasi-stationary states. Description of stable and unstable angina pectoris.

The following interpretation of the above considerations may be regarded as justified: in the mathematical model proposed, the first, stable branch of the root

$S = S_1^*$ can describe stable angina pectoris (if $S < S_{cr}$ for any s), whereas the second, unstable branch $S = S_2^*$ or any value of heart power h larger than h_{max}, corresponds to unstable angina pectoris. In the latter case any stationary state is not possible at all; such a state may be reached just as a result of decrease of heart power h or as a result of increase of the function $g(\tau)$, for example due to suitable therapy. Without decreased h or increased $g(\tau)$, we have at least for certain values of the coordinate s the derivative $dS/d\tau$, Eq. (4.2), always positive, leading to the critical state $\sup S = 1$, corresponding to a myocardial infarction. Actual history of unstable angina might be described just in probabilistic treatment.

As an example, the evolution equation (4.7) was integrated for the first set of numerical values of parameters ψ, S_0, and for the following program of external loading: $z = z_0$ for $0 < \tau < 0.1$ and $z = 0$ for $\tau > 0.1$ (external loading with constant power z_0 acts just in dimensionless time interval of the length 0.1; this is typical for weight-lifting). Five various values of this constant power were considered: $z_0 = 2, 3, 4, 5$ and 6. Numerical values of z_0 were chosen in such a way, as to evaluate the boundary value of z_0, separating healing from myocardial infarction, without drugs, and then with drugs. The results of integration for the initial condition $h_0 = 0.01$ for $\tau = 0$ are shown in Fig. 3: during the external

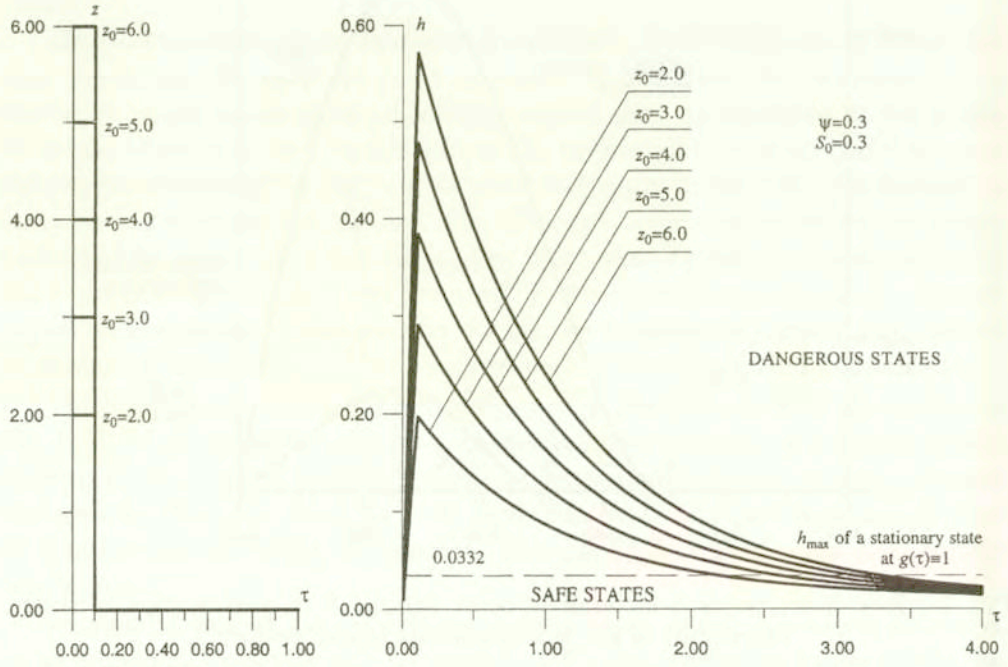

FIG. 3. Five programs of loadings and real heart power h in terms of time τ for these programs.

loading action, the required heart power h increases significantly and exceeds the admissible value of a stationary process, amounting here $h_{\max} = 0.0332$, and then monotonically decreases with time. Since $h_{\max}$ is exceeded, a myocardial infarction is possible. Indeed, the relevant integrals of the damage evolution equation (4.2) determining $S = S(\tau)$ without any therapy, $g(\tau) \equiv 1$, are shown in Fig. 4. Just in the case $z_0 = 2$ the infarction is avoided, whereas for larger values of z_0 we arrive at the value of damage $S = 1$ characterizing a myocardial infarction. The boundary value of z_0 separating AMI from healing without AMI amounts here to 2.39.

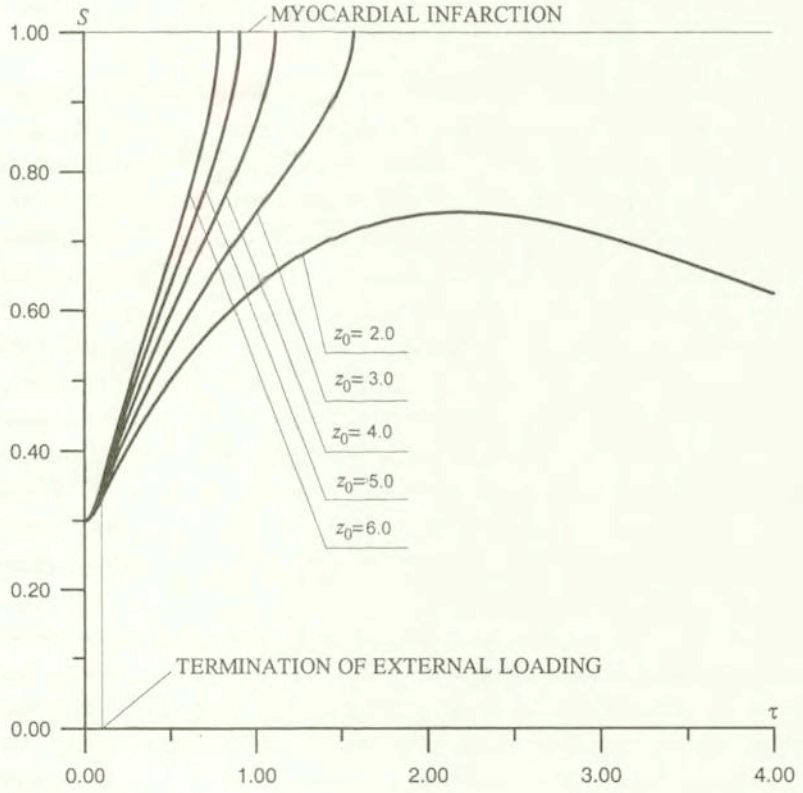

FIG. 4. Heart damage parameter S in terms of time τ without drugs.

8. Estimation of effects of drugs

According to the description given in the last section, the transition from stable to unstable angina and approaching a myocardial infarction depends in an essential manner on the modulus G, it means on the dimensionless function $g(\tau)$. Its value may be raised by taking drugs or by other forms of therapy (e.g. diet or

physical exercises). We propose here a description of the effect of drugs on the value of that function.

A small dosage of a suitably chosen drug (like nitrates which result in an increase of lumen) raises the value of the modulus, whereas excess dosage is, as a rule, harmful. For example, nitroglycerin protects the ischemic myocardium and limits the infarct size, but excessive doses may decrease the cardiac output, PASTERNAK *et al.* [27]. The simplest description of such effect can be obtained by using a quadratic function of masses of individual drugs

$$g(\tau) = 1 + \sum_{j=1}^{M} b_j m_j f_j(\tau - \tau_0) + \sum_{j=1}^{M}\sum_{l=1}^{M} b_{jl} m_j m_l f_j(\tau - \tau_0) f_l(\tau - \tau_0) \tag{8.1}$$

where M denotes the number of simultaneously taken drugs at the instant $\tau = \tau_0$, m_j – their masses, b_j – positive coefficients of the effect of unit mass of individual drugs, b_{jl} – coefficients of abuse of drugs and of their interaction. The quadratic form constituting the third term of the formula (8.1) must be negative definite, since practically always an effect of overdosage of medicines occurs. Hence all diagonal coefficients b_{jj} are negative, whereas off-diagonal coefficients b_{jl}, $j \neq l$, expressing interaction of individual drugs, may be positive in the case of mutually agonistic, and are always negative in the case of mutually antagonistic drugs (like beta-blockers and beta-stimulators). Non-negative functions $f_j(\tau - \tau_0)$ characterize the action in time of individual drugs taken at the instant $\tau = \tau_0$; as a rule, such a function reaches its maximum after some 10–30 minutes in the case of oral application, and after some 1–5 minutes in the case of intravenous or sublingual application, and then monotonically decreases practically to zero after several hours or days. Then a further dose should be taken, provided the heart power does not decrease accordingly.

One might also include into formula (8.1) negative effects, like nicotine; then the relevant coefficients b_j are negative.

An increase of the modulus G according to Eq. (8.1) raises the value $h_{\max}$, and can result in a return from nonstationary to the stationary state. In order to give a numerical example, the evolution equation (4.2) was integrated once more for the same set of parameters as in Sec. 7 and for the same loading program, but under the assumption that at the instant $\tau = 0.2$, in other words after a time twice as long as the period of action of external loading, suitable drugs were taken which resulted in a sudden increase of the value $g(\tau)$ from $g = 1$ to $g = 1.5$. The results of integration are shown in Fig. 5: evidently, for $\tau > 0.2$ the increase of damage S is smaller than in Fig. 4 and just in the case of maximal external loading under consideration, $z_0 = 6$, a myocardial infarction occurs. Now the boundary value of z_0 separating AMI from healing without AMI amounts to 5.34 and is over twice as large as in the case without drugs.

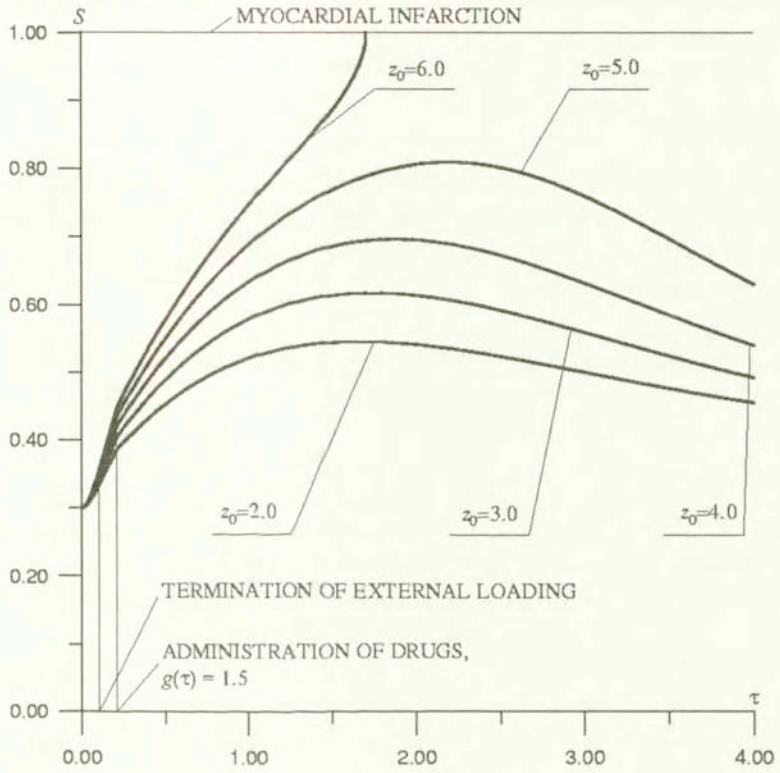

FIG. 5. Heart damage parameter S in terms of time τ with drugs taken at $\tau = 0.2$.

9. Conclusion

The description of coronary artery diseases and myocardial infarction given in the present paper has a phenomenological character and deterministic approach and hence – as it was mentioned above – it cannot reflect such phenomena as myocardial infarction resulting from fissuring of an atheromatous plaque or thrombus formation. It may constitute a first step towards a probabilistic approach describing phenomena of that type. Nevertheless, two basic evolution equations are proposed: that expressing the heart damage in terms of heart power, and that expressing the heart power in terms of power of physical and psychological external loadings. The mathematical model proposed seems to describe rather adequately basic features of development of the coronary artery disease, namely of atherosclerosis, vasoconstriction, stable and unstable angina pectoris, point of critical stenosis and myocardial infarction as a result of superposition of vasoconstriction on atherosclerosis; it considers also the effects of drugs. Evaluation of

necessary coefficients is at present difficult, but some directions of experinental research are also suggested.

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