causative factor and the degree of shock. Initially we have to prepare an X-ray of the chest, ECG, pO_2, pCO_2 of the arterial blood and the pH. Yet the only way to determine the state of haemodynamics is by performing the cardiac catheterization. Generally in every shock state we should provid e an adequate flow of blood via the coronary field, the kidneys, the liver, the nervous system, and the lungs. To reverse the progression of shock it is necessary to keep the mean arterial blood pressure 60 mm Hg or more. The lactate value should be below 22 mmol/l.

In case of the cardiogenic shock the situation is always very serious. The mortality rate in patients with cardiogenic shock during myocardial infarction reaches 90 %. Apart from the basic steps to handle shock we have to solve the problem of myocardial contractility and perfusion. The cardiac rhythm disturbances are other undesirable complication.

3.19 Septic shock and septicemia

When microorganisms and products of the inflammatory process reach the blood flow they might end up as a state known as **sepsis (septicemia)**. Septicemia is characterized by fever, rigor, tachycardia, tachypnoe, vasodilatation, and disturbances of consciousness at different levels. **When simultaneously with this there is a developing hypotension and hypo perfusion of organs** we name this condition as a state of **septic shock**. It has a very dramatic clinical symptomatology. Hypoperfusion is a result of a low vascular resistance, a low pumping function of the heart, and a disturbed micro circulation. Changes in the cardiac output in septic shock are known as the adapted compensatory mechanisms of shock. Hypoperfusion will lead to a diffuse cellular and tissue injury. Upon reaching a certain value the signs of multiple organ injury and failure become manifested. In this case and despite all the care given death can not be avoided.

Septicemia may result from all acute infections. Septic shock on the other hand usually occur in cases of infections caused by the **gram-negative bacteria**. Staphylococci, pneumoccoci, streptococci, and other gram-positive microbes are a less common cause of septic shock. Some viruses, mycobacterium, fungi and protozoa play a particular role in developing of septicemia. It is not easy to prove the presence of microorganisms the blood by (haemoculture). Even in a fully manifested septicemia haemoculture might not reveal any microorganisms in the blood.

According to trustful statistics, during one year in USA there is around 500 000 cases of septic shock caused by gram- negative bacteria. Mortality rate raches about 20 %. We are usually dealing with patients suffering of diabetes mellitus, liver cirrhosis, alcoholic patients, patients with leukemia, lymphoma, and disseminated carcinoma. Further they are patients - who undergo cytostatic and immunosupressive treatment and patients with neutropenia. It might as well occur in patients who are on the parenteral nutrition, in those having urinary tract infections and gastrointestinal infections including the gallbladder and the billiary tract. Another predisposed groups for septicemia are the new born and the elderly. Gram positive bacteria appear during the long lasting or repeated cathetarization and with long lasting antibiotic or glucocorticoid therapy. Previously there was a high incidence of post abortive and post puerperal sepsis as a result of endometrial and its surrounding structures invasion by streptococci. This condition was usually complicated by septic thrombophlebitis of the pelvis, peritonitis, or the formation of abscess.

The clinical manifestation of septicemia and septic shock are based on the **simultaneous action of microorganisms with the immune and the mediator systems** of the concerned organism. At the level of micro circulation a vicious circle develops between the decreasing tissue perfusion and the worsening of the endothelial quality. This results is tissue injury. If we don't interrupt this vicious circle the condition usually ends by death.

Among the most important microbial factors, that initiate the changes of septic shock are the lipopollysacharides of the gram-negative bacteria, specifically lipid A and peptidoglycans of the gram-positive bacteria. Even polysaccharides and extra cellular enzymes or toxins such as streptokinase and staphylococcal endotoxins can be manifested.

The mediators of the injured organ play a very

distinguished role in the pathogenesis of the septic shock. Those are mainly the active metabolites of the complement, kinin, and coagulation systems. Mediators such as **cytokines, TNF (tumor necrosis factor), interleukin-1, enzymes and oxidants from the polymorphonuclear leukocytes, vasoactive peptides, products of arachidonic acid metabolism** are released from the stimulated immunocompetent cells.

To antagonize the destructive action of the previously mentioned factors there will be a release of anticoagulants, catecholamins, angiotensin, hypophysial hormones, insulin, and glucagon.

Lipopolysacharides (LPS) of the gram-negative bacteria activate both the complement, kinin, and the coagulation systems at the same time (see fig. 3.21 on page 185).

The coagulation system and kinin system activation accomplished via the activation of Hageman factor. The cascade of coagulation then continues. Hageman factor changes prokalikrein to kalikrein (scheme). Bradykinin and other kinins increase the capillary permeability. The complement system activation takes place via the alternative way and results in C3a and C5a formation. These factors cause an increase of the capillary permeability and vasodilatation. Lipopolysacharides increase thrombocyte aggregation and their adhesion to the endothelial cells. Furthermore they enhance the release of the lyzozyme enzymes, and they activate the formation of super oxides.

Lipopolysacharides together with other bacterial products during sepsis stimulate the formation and the **release of interleukin-1 (IL-1) and tumor necrosis factor (TNF)** from macrophages, endothelial cells, and most probably from some other cells of the organism. IL-1 is responsible for the high body temperature (fever) during sepsis due to affecting the hypothalamic thermoregulation. It was shown experimentally that the application of TNF to experimental animals evokes similar changes to those changes accruing in septic shock. After the application of TNF we will notice the appearance of hypotension, an injury to the lungs and pulmonary circulation with the formation of leucocytic and thrombocytic thrombi, intestinal haemorhagic necrosis, acute renal failure, metabolic acidosis and animal death. Glucocorticoids block the effect of TNF and even the effect of IL-1. In normal subjects we notice the appearance of TNF in the plasma post LPS application. It was proven clinically that there is a close correlation between the value of TNF, and the serious of shock and the mortality. Yet the correlation between the TNF value and the IL-1 level is less prominent. TNF and IL-1 act synergeously even in the experimental conditions.

They liberate lipids from the adipose tissue and they cause hyperlipidaemia. They stimulate hepatic glycogenolysis and gluconeogenesis. Furthermore they inhibit the synthesis of albumin and hence leading to hypoalbuminaemnia. TNF and IL-1 liberate glucagon and insulin from the pancreatic cells, ACTH from the hypophysis as well as beta endorphins, growth hormone, and ADH.

In experimental conditions it was found that by inhibiting cyclooxygenase or thromboxan synthesis it is possible to inhibit the progression of the septic endotoxic shock. The level thromboxan B_2 (TXB_2) and the end product of the prostacyclin metabolism 6-keto-prostaglandin F_1 alfa, found to be high in patients with sepsis. Thromboxan produced by activated thrombocyte and polymorphonuclear leukocytes act as thrombocyte aggregating substance, and apart from this they stimulate pulmonary vasculature vasoconstriction. Prostacyclines produced by the endothelial cells antagonize the effect thromboxans. Prostacyclines act as vasodilatation agents and they increase capillary permeability. The formation of these substances as well as the formation of classical prostaglandins of the E series by different cell might be induced by interleukin-1 and TNF or even LPS. Circulating PGE_2 act as a vasoconstrictor and it potentiate and increase the gastrointestinal motility.

LPS has a direct effect on polymorphonuclear leukocytes, thrombocytes, macrophages, and most cells. They increase the formation of leukotriens and platelet activating factor (PAF) in these cells. Leukoteriens may predispose to pulmonary edema. PAF cause thrombocyte aggregation, vasodilatation, and increases the permeability of the capillaries.

Endothelial cells and microcirculation are buffers for the released substances and the on going destructive processes. This is provided by pre capillary blood shunts and post capillary venule obstruction by polymorphonuclear leukocytes, thrombocytes thrombi, and fibrin deposits. A generalized condition known as the fenestrated capillary syndrom is usually manifested by pulmonary

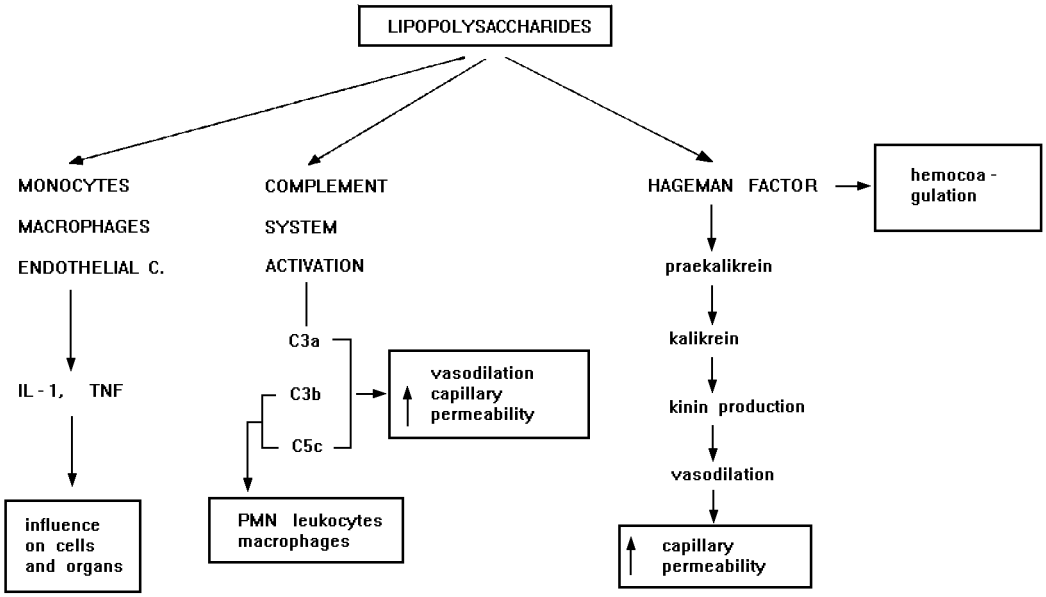

Figure 3.21: Effect of lipopolysacharides in septic shosk

oedema. Kinins, C3a, C5a, histamin, arachidonic acid metabolites, protease and oxygen radicals all take part on the vasomotor injury of the large vessels and capillaries. Tissue hypoxia and cellular death is the end result of the micro circulatory disturbance.

The cardiovascular changes in septicemia and septic shock differ from the cardiogenic hypovoleamic shock by the fact, that in septic shock the peripheral (vascular) resistance is low whereas the minute cardiac output is high. The disturbed microcirculation on the non rational distribution of blood are the result of many simultaneously acting vasodilatatory and vasoconstricting factors. The capillary leak of fluid ends up by hypovolemia. A refractory hypotension and a continuously low peripheral vascular resistance worsens the already present acidosis this eventually leads to multiple organ injury and finally death occurs. The pulmonary circulation changes accordingly depending on the level of pulmonary edema, the degree of hypoxia and acidosis. The destruction reveals ARDS (adult respiratory distress syndrom).

The plasma concentration of lactate increases from the beginning of sepsis. Lactate is produced by hypoperfusion tissues. The progressing vasoconstriction and renal and hepatic failure prominently worsens lactic acidosis. Hypoxia becomes deeper even due to pulmonary complications. There will be formation of pulmonary edema, hemorrhages, and capillary thrombi.

Thrombocytopenia is a common accompanying symptom of septicemia. It results from a direct LPS action, and thrombocyte activation (aggregation). The simultaneous activation of Hageman factor has its share in the formation of disseminated intravascular coagulation.

Renal hypoperfusion can end up by acute renal failure. The renal injury is initially presented as oliguria, azotemia, and proteinuria. The development of tubular necrosis may occur later on.

Loci of necrosis may be formed **in the myocardium** and they may lead to heart failure. In the intestines there might be some haemorhagic necrosis. In the end stage hepatic necrosis develops. The clinical manifestation of septic shock were mentioned previously. Fever and chills are not a condition in the clinical manifestation of the septic shock. In some patients a raise in temperature is not found at all (anergia). These are usually elderly patients, alco-

holics, and uremic patients. This condition always carries bad prognosis.

Septicemia with **disseminated intravascular coagulation** is usually accompanied by acrocyanosis and necrosis of the peripheral sites of the body. In some patients we may notice an initial nausea, vomiting, diarrhea or ileus. An upper GIT bleeding may appear.

If septic shock takes place in patients with another serious disease the prognosis is always bad. Mortality due to septic shock is about 25 %. The highest mortality occurs within the first 48 hours, and is caused by the irreversible shock with all its drawbacks.

3.20 Etiopathogenesis of atherosclerosis

In the last 40 years **cardiovascular diseases** are in all economically developed countries of the world the major cause of morbidity and mortality. Their substantial part is due to atherosclerosis. In our country the number of these diseases continues to increase in contrast to countries such as USA or Sweden where this number has been already decreasing for several years. The consequences of atherosclerosis in our country cause about 56 % of all deaths in the age between 35 to 65 years, i.e. in the working productive population. Furthermore, their occurence is shifting towards younger age groups. From the point of view of **pathological anatomy** the basis of atherosclerosis is a focal accumulation of lipid substances and an increased amount of connective tissue components within the arterial intima resulting in a subsequent oringin of focuses of pulpy fat-tissue debris known as atheromatous plaques. These plaques protrude into the arterial lumen and cause its narrowing. Within the atheromatous calcium salts may be deposited later (calcificated plaques). The consequence is a substantial loss of the arterial wall elasticity so that the arteries are no more able to allow for an increased blood flow during higher oxygen demands of the tissues.

The endothelium damage and the blood flow turbulence in the place of atheromatous plaques create conditions for **the mural trombus formation**. This trombus gets organized with time but with the repeated occurence of this process it in fact extends and progressively narrows or acutely occludes the artery.

In advanced stages of atherogenesis the atheromatous plaques undergo some relevant changes, e.g. disruption ulceration (cell necrosis on the top of the plaques), or intraplaque haemorrhage and intramural haemorrhage into the surrounding artery wall. Plaque disruption and ulceration considerably increase the disposiotion to the formation of superficial thrombi. Intramural haemorrhage also produces acute narrowing of the artery lumen. Advanced plaques affected by these changes, i.e. **calcification, ulceration, haemorrhage and thrombosis** are so-called "complicated atheromatous lesions". Only in this stage of atherosclerosis a clinically significant occlusion of the artery followed by ischaemia of the supplied region originates. Complicated atheromatous lesions may crumble and the pulpy fat-tissue debris and other constituents of the plaques may get loosened into the lumen of the artery and may be a source of microembolisation.

Atherosclerosis affects mostly aorta, elastic and elastic-muscular type of arteries (large and medium size arteries). Atherosclerotic lesions may develop separately only in one vessel region (e.g. in aorta, in coronary carotid, cerebral, legs, renal, or mesenterial arteries), or it may be a diffuse affection of the whole arterial system (generalized atherosclerosis). The affections of the coronary (ischaemic heart disease followed by myocardial infarction), cerebral (haemorrhage or encefalomalacy) and lower extremities (gangrene) arteries are the most frequent occurances with serious clinical consequences.

In conclusion, atherosclerosis is a long-term, very complicated and complex pathological process causing lesions of the arterial wall. It is asymptomatic for a long period of time and gets clinically manifest only when complicated atheromatous lesions occur. **Clinical consequences** of atherosclerosis appear particulary because of the occlusion of the corresponding artery, or sometimes because of the aneurysmatic dilation of the artery (an atheromatous lesion of the arterial wall leads to its weakening, which causes an aneurysm formation). Clinical symptoms differ according to the affected organ, or part of the vascular region.