Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage

Michel E. Safar1 and P. Lacolley2

1Paris-Descartes University, Faculty of Medicine; Hôtel-Dieu Hospital, Diagnosis Center Assistance Publique-Hôpitaux de Paris, Paris, France; and 2Faculté de Médecine de Nancy, Nancy University, Nancy, France

Safar ME, Lacolley P. Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage. Am J Physiol Heart Circ Physiol 293: H1–H7, 2007. First published March 16, 2007; doi:10.1152/ajpheart.00063.2007.—Whereas large arteries dampen oscillations resulting from intermittent ventricular ejection, small arteries steadily deliver optimal blood flow to various organs as the heart. The transition from pulsatile to steady pressure is influenced by several factors as wave travel, damping, and reflections, which are mainly determined by the impedance mismatch between large vessels and arteriolar bifurcations. The mechanism(s) behind the dampening of pressure wave in the periphery and the links between central and peripheral pulsatile pressure (PP) may determine cardiac damage. Active pathways participate to pulse widening and changes in pulse amplitude in microvessels. Steady and cyclic stresses operate through different transduction mechanisms, the former being focal adhesion kinase and the latter being free radicals and oxidative stress. Independently of mechanics, calcifications and attachment molecules contribute to enhance vessel wall stiffness through changes in collagen cross-links, proteoglycans, integrins, and fibronectin. Enhanced PP transmission may thus occur and precipitate organ damage at each time that autoregulatory mechanisms, normally protecting the heart from vascular injury, are blunted. Such circumstances, observed in old subjects with systolic hypertension and/or Type 2 diabetes mellitus, particularly under high-sodium diet, cause cardiac damage and explain why increased PP and arterial stiffness are significant predictors of morbidity and mortality in the elderly.

microvessels; end-organ damage

CARCIN COMPLICATIONS, a major cause of mortality, are traditionally attributed to alterations of the cardiac pump and/or to intrinsic modifications of myocardial cells. The damage due to changes in arterial and arteriolar alterations is less frequently taken into consideration to explain cardiac events. The goal of this report is to summarize the principal consequences of a disturbed macro- and microcirculation on cardiac mortality. A necessary prerequisite for this purpose is to define in humans the principal characteristics of arterial and arteriolar functions.

The major goal of large arteries is to deliver an adequate blood supply from the heart to peripheral tissues, as dictated by metabolic activity. Conduit-function efficiency, which is the consequence of the width of the arteries and their very low resistance to flow, is primarily dependent on the diameter of the arterial lumen, which reacts to endothelial function and shear stress (30, 31). Atherosclerosis, which is the most common vascular disease disturbing conduit function, is considered to dominate cardiovascular (CV) risk in each individual (30, 31).

In addition to conduit function, large arteries have a cushioning function that consists to dampen the pressure oscillations resulting from intermittent ventricular ejection and to transform the pulsatile flow of arterial vessels into the steady flow required for oxygen supply. The efficiency of cushioning function depends on the viscoelastic properties of arterial walls and the vascular geometry, including diameter and length. Stiffening of arterial walls results in an increase of systolic (SBP) and a decrease of diastolic (DBP) blood pressure (BP) and therefore a high pulse pressure (PP). PP, arterial stiffness, and central wave reflections are independent predictors of CV risk, particularly for CV diseases and mainly for myocardial infarction (30). Increased PP is associated with higher SBP, which promotes cardiac hypertrophy, and with decreased DBP, which favors myocardial ischemia. The pathophysiological consequences of defective cushioning function, which differ consistently from those observed in subjects with atherosclerosis, affect mainly the heart and coronary vessels and thus are mainly located upstream. In contrast, the downstream consequences of defective cushioning function have been poorly explored in the literature (23, 26, 27, 30, 31). In many situations, such as those observed in diabetes mellitus and systolic hypertension, a microvascular disease is observed in the elderly, in association with end-organ damage affecting the kidney (proteinuria and chronic renal failure), the brain (retnopathy and/or dementia), and/or the heart (coronary ischemia without evidence of atherosclerosis) (23). In most of these situations, the contribution of PP, arterial stiffness, and wave reflections in the mechanism(s) of end-organ damage has not been extensively explored.
The purpose of this review is to determine, in the mechanism of CV risk, the possible consequences of heightened PP, arterial stiffness, and wave reflections on macro- and microvessels and to evaluate in which situations such alterations may affect CV risk of vital organs, including the heart. Our working hypothesis is that, particularly in the elderly, PP may be transmitted to microvessels in each circumstance where the blood flow autoregulatory mechanisms normally protecting vital organs are offset. After the principal basic concepts on macro- and microvessels have been defined in this review, the two main questions will be: first, how may an exacerbation of PP widening be observed in the elderly? Second, why and how could the autoregulatory mechanisms normally protecting the brain, the kidney, and mainly the heart be offset?

**Basic Concepts on Macro- and Microvessels**

Because this report requires an analysis of the principal factors modulating the transition between pulsatile and steady pressure along the arterial tree, it is necessary to summarize (Fig. 1) the most traditional structural and functional aspects of the macro- and microcirculation in humans. It is worth noting that arterial diameter in the microvascular network is considered to be below the value of 150 μm (23, 27).

**Pulsatile pressure and large arteries.** Following ventricular ejection, BP propagates along the arterial tree as a wave (Fig. 2). At each discontinuity of the arterial wall, this wave may be “reflected” and then becomes retrograde (30, 31). Arteriolar branching is considered to be the main sites of wave reflections (Fig. 2). As a consequence of the summation of incident and reflected waves at each discontinuity of the arterial wall, SBP and PP are physiologically higher in peripheral than in central arteries, whereas mean arterial pressure (MAP) and DBP remain practically unchanged along the arterial trajectory. For each given artery, the summation of the forward and the reflected wave is influenced by several factors (Fig. 2): the velocity of the wave [i.e., pulse wave velocity (PWV); the higher the PWV, the higher the arterial stiffness], the degree of arterial lumen diameter mismatch with amplitude reflection (small diameter results in higher amplitude), and the aortic length (wave reflection is closely correlated with arterial length and hence body height). In young, healthy, tall subjects, the wave summation takes place low in the abdominal aorta, in early diastole, thus boosting the diastolic coronary perfusion without disturbing cardiac afterload (30, 31). A stiffer aorta with greater PWV, aortic branches with smaller lumen diameters, and shorter stature cause the reflections to occur in late systole (rather than in diastole as in healthy individuals). Under this condition, i.e., with the pressure wave occurring earlier and closer to the aortic valve and coronary sinuses during systole, coronary perfusion is impaired, leading to myocardial ischemia. SBP is augmented through an additional increase due to wave reflections. These are classical situations, particularly observed in diabetic and elderly subjects, where systolic hypertension is frequently present (23, 26, 27, 30, 31). Finally, it appears that the particular site of each vessel branching and the geometrical characteristics of each resistance vessel are critical points for the understanding of increased SBP, PP, end-organ damage, and their relationships.

**Steady pressure and microvascular network.** At the end of the arterial system (diameter < 150–158 μm), the complex network of small arteries and arterioles represents the resistance vasculature in which a nearly steady flow is achieved. Accordingly, a small but consistent loss in pressure gradient is noted from larger to smaller arteries, including capillaries (31). Finally, a very low intraluminal pressure is obtained, which is necessary for capillary exchanges. This requires, according to age, adaptive changes of the microvascular network, as well as in normotensive, hypertensive, or diabetic populations. According to the Poiseuille’s law, these changes may affect the viscosity of blood, the diameter of individual microvessels, but also their length and their number (density), with wide variations according to each organ, particularly the heart.

Classically, the changes in vascular resistance observed from the conduit arteries to the microcirculation occur very abruptly over the short distance of the path between arteries and veins (Fig. 3). The very high resistance over a short pathway is mainly located in prearteriolar vessels and causes MAP to fall precipitously over this distance (15, 30). Thus high resistance is associated with a reduction of both pulsatile phenomena and steady flow (Fig. 3), resulting in quasi-total steady flow through resistance vessels. Arterial pulsations that cannot enter high-resistance vessels are reflected and combined with pressure waves approaching the area of high resistance, thereby contributing to the occurrence of backward pressure wave (30, 31). Finally, through the control of pressure-induced arteriolar myogenic tone, the circulations of the main organs, such as the brain, the heart, and the kidney, are normally highly protected from the systemic BP changes, which initially in-
volve both a steady and a pulsatile component (Figs. 2 and 3). In this review, the complete description of myogenic tone as well as of organ autoregulation (23, 27, 30) will be considered as out of the scope of the study.

Age, PP, and autoregulatory mechanisms protecting the brain, heart, and kidneys from organ damage. The hemodynamic model described in this report is well adapted to the understanding of normal capillary exchanges and to the pathophysiological mechanisms resulting from increased cardiac load. This model cannot adequately describe in which conditions a defective cushioning function may have downstream deleterious consequences on microvessels and finally affect vital organs, such as the brain, the heart, and the kidney.

An increase in arterial stiffness with age, which was in the past considered as uncommon in acculturated societies (30, 31), is nowadays constantly observed in industrialized countries and even studied as a “physiological” phenomenon. With age, the increased stiffness, which initially predominates on central large arteries, affects the pressure wave of all systemic arteries (23, 27, 30, 31). Since the incident and reflected waves summate and are additive, a general rise of SBP and PP throughout arterial system is observed (30). Pressure wave contour and amplitude become similar in all arteries and then reach peripheral organs. Recent data have shown that, in healthy cohorts with a minimal burden of CV risk factors, a “physiological” age-related increase in aortic stiffness, compared with peripheral arterial stiffness, is associated with an increasing forward wave amplitude and PP, with even reversal of the arterial stiffness gradient (26). Thus, with aging, together with the presence of endothelial dysfunction and oxidative stress, there is a facilitation of the forward transmission of pressure pulsations into the peripheral organs, with potential deleterious consequences. This hemodynamic profile may be particularly relevant to consider for the kidney (30).

The diffusion of pulsatility, which nowadays has been observed much deeper than it was thought in the past (23, 27), may occur very close to the heart, the brain, and the kidneys, depending not only on age but also on the site and the characteristics of each organ. For instance, whereas the perfusion of coronary arteries occurs exclusively during the diastolic time, the brain and the kidney receive relatively high flow at rest during both systole and diastole. For these simple reasons, the key arterial segments in which blood flow is changed from pulsatile to steady flow may differ according to the geometry and structure of each vascular territory. As far as the mechanism(s) of myogenic tone is (are) concerned, it is worth noting that myogenic tone differs from flow dilation, particularly regarding the role of endothelial function and control of...

![Fig. 2. Propagation of the pressure wave along the arterial tree. Propagation needs a given velocity [pulse-wave velocity (PWV) as in 1]. Reflections mainly occur at the sites of arteriolar branching points (2). The blood pressure (BP) curve represents the summation between the forward and the reflected waves (3) (see Refs. 30 and 31).](image)

![Fig. 3. Description of the transition from the pulsatile to the steady pressure (see Refs. 30 and 31). Left: physiological BP changes. Right: modelization of the system. Curves 1 and 3 represent the normotensive and hypertensive curves, both leading to the same low capillary pressure. To avoid an increased capillary pressure (as in curve 2) in hypertension, an adaptation of the mechanosensitive vasomotor function of endothelium is required (arrow; see Ref. 15).](image)
Invited Review

PULSE PRESSURE AND ORGAN DAMAGE

H4

of both systemic MAP and the amounts of elastin and collagen stimulus (30, 31). Furthermore, calcifications and attachment becomes stiffer in the presence, than in the absence, of pulsatile arterial wall through transduction mechanisms independent of

Mechanisms of PP Extent and Diffusion

In recent years, it has been shown that PP interacts with the arterial wall through transduction mechanisms independent of MAP. Indeed, at any given value of MAP, the arterial wall becomes stiffer in the presence, than in the absence, of pulsatile stimulus (30, 31). Furthermore, calcifications and attachment molecules are able to increase arterial stiffness independently of both systemic MAP and the amounts of elastin and collagen within the vessel wall (30).

Cyclic mechanical factors and the arterial wall. Since the pioneering studies of Glagov (10), many investigations (12, 21, 30, 31, 35) have studied the effect of cyclic forces on the arterial wall, particularly on endothelial cells exposed to pulsatile shear stretch in vitro (12, 21, 30, 31, 35). The role of cyclic shear stress (as opposed to steady stress) and the importance of stimulus duration and graded responses to mechanical forces have been investigated, particularly regarding nitrite oxide and super oxide anions (12). Cyclic mechanical strain has also been examined, mostly in cultured vascular smooth muscle (VSM) cells. Long-term cyclic distention enhances the mechanical properties of collagen-based medial components and even heightens collagen and fibronectin (FN) accumulations in animal or human VSM models (12, 21, 35). The vessel/wall materials become stronger and stiffer than those obtained under static conditions.

A distinct feature of VSM cells is their phenotypic plasticity, particularly during the transition from the contractile to the synthetic phenotype of VSM cell cultures in the absence of mechanical forces (21). Exposing cultured VSM cells to cyclic stretch can restore the expression of high-molecular weight caldesmon and other markers of differentiated VSM cells. A certain degree of stretch is necessary for the preservation of the VSM contractile state (21). Hence, the failure to maintain a threshold level stretch is likely to contribute to VSM cell transformation.

Stretch initiates complex signal transduction cascades leading to gene transcription and functional responses via interaction of integrins with extracellular matrix proteins or by stimulation of G protein receptors, tyrosine kinase receptors, or ion channels (reviewed in Ref. 3). The intracellular pathways reported to be activated by cyclic stretch in VSM cells include mainly the mitogen-activated protein kinase cascades and nuclear factor-κB (21, 30), which have been studied at both VSM and endothelial levels. More recently, steady and cyclic modes of stretch have been shown to transduce differently in the aorta, the former implicating focal adhesion kinase and the latter free radicals as derived from oxidative stress and the presence of inflammatory factors (19, 20) (Fig. 4).

Finally, the transcriptional profile of mechanically induced genes in VSM cells subjected to a uniform biaxial cyclic strain has been studied (18). Cyclic stretch was found to stimulate the expression of a number of genes, including vascular endothelial growth factor and plasminogen activator inhibitor-1, but to negatively regulate others, such as extracellular matrix metalloproteinase-1 and thrombomodulin.

Nowadays, the differential effects of steady and pulsatile forces should be considered as obvious, even if several of them have been investigated only in vitro (12, 21). The corresponding in vivo findings remain scarce. Most of them are simply deduced from human epidemiological investigations, indicating that pulsatile stress, as represented by PP, wave reflections, and/or arterial stiffness, is a more adequate predictor of CV risk than steady stress. In humans, steady stress is traditionally represented by the height of brachial SBP or DBP (30).

Stiffness of wall material, calcifications, and attachment molecules. In recent years, studies on rodents have shown that, particularly in old age, with diabetes mellitus, and/or in subjects on a high-sodium diet, arterial calcifications (not described in this review) and attachment molecules (between VSM cells, or VSM cells and extracellular matrix proteins, or between collagen fibers) contribute per se to stiffen the vascular wall (2, 30).

Cross-links may stabilize collagen fibrils, preventing slippage of adjacent molecules under applied tensile stress (30) and contributing to increased arterial stiffness through formation of end-glycation products (34). In elderly subjects with systolic hypertension, drugs involving collagen cross-link breakers acutely reduce arterial stiffness and PP without any change in MAP (34). Glycosaminoglycans exhibit viscoelastic properties, which make them good candidates as flow-sensing molecules, binding sodium and calcium ions in their helicoidal chains (1). Removal of 65% of chondroitin-dermatan sulfate-containing glycosaminoglycans from mesenteric resistance arteries increases their stiffness (8). In carotid arteries of spon-

Fig. 4. Schematic representation of the different pathways of mechanotransduction for steady and pulsatile stretch (19, 20). The representation is over-simplified but obviously shows that the two mechanisms of stretch differ consistently, FAK, focal adhesion kinase; ROS, reactive oxygen species; MAP, mean arterial pressure (see Refs. 19 and 20).
taneously hypertensive rats (SHR), a chronic high-sodium diet results in a reduction in arterial hyaluron and enhanced aortic stiffness (6).

Because integrins transmit inside-out and outside-in signals capable of modulating vascular responses, Lacolley and colleagues (2) suggested that adhesion molecules, such as FN and its integrin receptor(s), might contribute per se to change arterial wall stiffness (2). FN-matrix polymerization increases tensile strength of model tissue (9). In young and old SHR, measurements of aortic FN indicate that an increased number of attachment sites between VSM cells and extracellular matrix proteins may contribute to enhance arterial rigidity (2). On a normal sodium diet, angiotensin-converting enzyme inhibition (ACEI) reduces MAP and PP, together with a reduction in aortic FN and $\alpha_\text{SB1}$ integrin and an increase in isobaric arterial distensibility (16). With ACEI plus a high-sodium diet, MAP is significantly reduced, but PP and arterial stiffness, as well as aortic FN, remain enhanced. Similar results have been obtained when chronic administration of aldosterone is combined with a high-sodium diet in Sprague-Dawley rats (17). In this latter experiment, the enhancement in FN and stiffness are reversed by an administration of the selective aldosterone antagonist eplerenone (17).

In conclusion, local changes in the attachments between VSM cells and extracellular matrix, as well as arterial calcification, may independently modulate the stiffness of each artery taken individually. All these pathophysiological mechanisms also contribute to the development of new sites of wave reflections. Finally, the extent of disturbed arterial stiffness and wave reflections in each individual subject is largely influenced by the vascular territories involved and by the patient’s age. In some cases, as in subjects with obesity and/or insulin resistance, arterial stiffness is increased with minor changes in wave reflections (30, 31). In most cases, both parameters are increased in parallel. For all patients, bidirectional interactions develop between increased PP and enhanced wall stiffness, thus creating a vicious circle and increasing the risk of CV complications (30, 31).

PP, Arterial Stiffness, and Cardiac Damage

In the coronary circulation, autoregulation is a quite powerful process protecting the heart, exactly as in the renal and cerebral circulations (28). However, there are two main particularities. First, in old people and in subjects with hypertension and/or atherosclerosis, the coronary reserve is markedly reduced very early. This situation, which affects primarily the arteriolar and prearteriolar resistance of the coronary circulation, may also alter consistently the capillary network. Second, because of the constantly contracting effect of cardiac muscle, the coronary perfusion pressure is represented exclusively by DBP, and not by MAP, as in the totality of the other organs as the brain and the kidney.

Within the heart, capillary pressure is, in general, very difficult to determine, so cautious interpretations are necessary. However, it is generally admitted that capillary hydrostatic pressure should be considered to be held constant at all times (23). The coronary arterioles (ranging in size from 150 to 300 $\mu$m) act as the main resistance vessels (4, 14). The capillaries are very small but, at least in some models, offer an additive role of high resistance to flow. Because they are arranged in parallel, the total capillary resistance may decrease markedly with the increasing number of capillaries (14).

When hyperemia is induced in the normal coronary circulation, smooth muscle relaxation results in dilatation of the arterioles and venules with little change in the capillaries (14). The total myocardial vascular resistance decreases and, because of the similar decreases of arterial and venular resistances, the capillary hydrostatic pressure remains largely unchanged (14). However, under such circumstances, the specific contribution of capillary resistances in the total myocardial vascular resistance may become very high. Thus capillaries may generate the most resistance to coronary blood flow during hyperemia and even define an upper limit to the effects of this hyperemia (14). Because they lie in parallel, the more numerous the capillaries, the higher the hyperemia, and, vice versa, the fewer the numbers of capillaries, the lower the hyperaemia (14, 23). Because, in several circumstances, cardiac hypertrophy is present, the intercapillary distance is widely augmented and contributes to myocardial hypoperfusion and to a reduction of oxygen delivery (11, 23). Finally, conditions associated with fewer capillaries (either anatomically or functionally, as for instance, under high-sodium diet), such as observed in myocardial infarction, hypertension, or diabetes, are also associated with reduced coronary reserve even in the absence of coronary stenosis (23, 33). In recent years, therapeutic programs in rats models have confirmed the respective contribution of arterioles and capillaries in the mechanism of neovascularization of coronary and leg arteries (24, 33). In cardiac models, ACEI by perindopril alone increases only arteriolar density, whereas the diuretic indapamide increases only capillary density. Exclusively, the combination of both ACEI and diuretic improves the density of the total microvascular network (arterioles and capillaries). Such results fit well with the opposite effects that are widely observed on cardiac microvessels under high-sodium intake, administration of angiotensin II, or their combination (7, 11).

From a clinical viewpoint, when coronary reserve is markedly reduced, the almost unique hemodynamic factor determining coronary perfusion remains aortic DBP, particularly in subjects with coronary atherosclerosis (13). A low DBP favors myocardial ischemia as a consequence of either low systemic vascular resistance or increased arterial stiffness or a combination of both factors (30, 31). In subjects with hypertension, drug treatment markedly reduces systemic vascular resistance and hence MAP and DBP. In contrast, drug treatment has little effect on arterial stiffness, which increases “physiologically” with age, independently of changing MAP and vascular resistance. Thus, as a consequence of an age-induced increase of arterial stiffness, aortic DBP and coronary blood flow tend to fall (22), whereas SBP and PP rise in parallel, thus favoring the development of cardiac hypertrophy (30, 31). Finally, the deleterious effects of increased PP on the heart completely differ from that of PP on the brain and the kidney (28). Because of the exclusive diastolic perfusion of the heart, increased SBP is not transmitted to microvessels but only contributes to enhance the size of myocardial cells. The low DBP, on the other hand, markedly affects myocardial perfusion. Finally, cardiac hypertrophy is associated with an increased intercapillary distance, which is associated with reduced oxygen delivery, particularly in the subendocardial territory (13, 23). Probably for all these reasons, the drug treatment of hyperten-
sion prevents myocardial infarction, but less successfully than stroke (30, 31).

Prospective Views

The transition of pulsatile pressure and flow from larger to smaller arteries is traditionally conceived as a pure adaptive phenomenon, mainly due to the progressive and passive narrowing of the vessels and contrasting with powerfully active autoregulatory mechanisms protecting vital organs as the brain, kidney, and heart. With age and under several pathophysiological situations as those observed in diabetes mellitus, systolic hypertension, and high-sodium diet, active mechanisms develop and contribute to associate increased arterial stiffness, widened PP, and defective protection of organ blood flow autoregulatory mechanisms. Even in the presence of normal steady pressure, enhanced BP transmission results from increased PP and finally determines cardiac damage. For the heart, this situation is particularly complex since the cardiac intermittent contraction is responsible per se for both increased PP and coronary perfusion exclusively in diastole. However, for the heart as for all varieties of end-organ damage, the same consequence occurs: a hypoperfusion of the corresponding organ. This alteration is in turn exacerbated by the presence of capillary rarefaction, which predominates in hypertrophied (the heart) much more than in atrophied (the kidney and brain) organs.

This report has also shown that all these mechanisms have a common denominator: the presence of a defect in the elasticity of the CV tissues. This finding reflects modern aspects of CV epidemiology in which not only atherosclerosis and the heights of SBP and DBP are predictors of CV risk but also other CV mechanical factors involving the macro- (arterial stiffness, wave reflections, and PP) (30) and microcirculation (structural changes of the arterioles) (29).

ACKNOWLEDGMENTS

This study was performed in relation with Institut National de la Santé et de la Recherche Médicale and Groupe de Pharmacologie et d’Hémodinamique Cardiovasculaire (Paris, France). We thank Dr. Anne Safar for pertinent discussions.

REFERENCES