Drug Disease Interactions: Role of inflammatory mediators in disease and variability in drug response

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ABSTRACT Expression of both pro- and anti-inflammatory mediators are influenced by various factors such as rheumatic diseases, myocardial infarction, angina, aging, obesity and pharmacotherapy. This has therapeutic consequences. Clearance of highly bound and efficiently metabolized drugs may be reduced in the presence of inflammation amounting to increased circulating drug concentration. In the meantime, various cardiovascular receptors are down-regulated in the presence of pro-inflammatory mediators. Consequently, conditions such as rheumatoid arthritis, aging and obesity results in reduced response to drugs such as verapamil despite increased drug concentration. The inflammatory response is a complex cascade of non-specific events resulting in excessive generation of inflammatory mediators such as cytokines, C-reactive protein and nitric oxide by cells of the innate (macrophages, monocytes, neutrophils) and adaptive (T-lymphocytes) arms of the immune system. T-lymphocytes secrete various pro- and anti-inflammatory cytokines during an inflammatory event. In general, two distinct subpopulations of these T-helper cells exist, anti-inflammatory Th2 and pro-inflammatory Th1. As a common rule, Th1 cytokines suppress Th2 and vice-versa. Hence, a balance of these activities is desired. Drugs such as antirheumatoid agents, angiotensin II blockers and hydroxymethyl-glutaryl-CoA reductase inhibitor (statin) may help to restore the Th1/Th2 balance. In general, at least for some conditions, the challenge of therapeutic drug monitoring will be more useful if expression of inflammatory mediators is also taken into account. In addition, some of the intersubject variation in pharmacotherapy and clinical trails may be attributed to variations in the inflammatory mediator's concentration. A detail list of conditions and drugs that influence expression of the inflammatory mediators are provided and potential therapeutic consequences are discussed.

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INTRODUCTION

The inflammatory response is a complex cascade of non-specific events stimulated by infection or tissue damage (1). This usually is a well-controlled process. However, excessive generation of inflammatory mediators such as cytokines, C-reactive protein (CRP) and nitric oxide (NO) by cells of the innate (macrophages, monocytes, neutrophils) and adaptive (T-lymphocytes) arms of the immune system can result in disease (1, 2). T-lymphocytes (cells) secrete various pro- and anti-inflammatory cytokines during an inflammatory event resulting in outcomes ranging from elimination of pathogens to allograft rejection (3-5). Involvement of T-cells during inflammation is dependent on the population of activated cells. Briefly, CD4+ T cells conduct adaptive immune responses in reaction to foreign antigens. In general, two distinct subpopulations of CD4+ T helper cells exist due to unique cytokine arrays produced. These are the T-helper 1 phenotype (Th1) and the T-helper 2 phenotype (Th2). Th1 cells predominantly produce IL-2, IFN-γ and TNF-α. These cytokines induce cellular immune responses and activate macrophages. The Th2 phenotype mainly produces IL-4, IL-5, IL-10 and IL-13 that are important in aiding B cell activation and antibody production. As a common rule, Th1 cytokines suppress Th2 and vice-versa. Thus, once a particular T helper cell immune response is established (Th1 or Th2), the polarized sub-type tends to persist through positive feedback mechanisms (6-11). Expression of specific cytokines by T-helper cells results in Th1 and Th2 cell dominant inflammatory disorders (12, 13).

Cytokines are a diverse group of soluble messenger proteins involved in the activation, growth, control and repair of cells and regulation of immune events (2, 9). Cytokines may act within the same cell (autocrine), nearby (paracrine) or at distant sites (endocrine) (1, 2). Strict regulation, transient production, and binding to cell surface receptors normally occurs with redundancy and pleiotropy observed (14, 15). The pleitropic nature results from many cells having receptors for the same cytokine

and the overlapping function of cytokines creates redundancy leading to formation of networks with cascade responses. Sequential expression due to cytokine cascades occurs in many conditions, for example, in rheumatoid arthritis, IL-1, -6, -8 and granulocyte macrophage-colony stimulating factor are expressed downstream of TNF-α (16,17). Other conditions in which cytokine cascades are reported are congestive heart failure, multiple myeloma and sepsis (18-20). Cytokines e.g., IL-1, -2, -6, -12, -18, TNF-α, -β (lymphotoxin), interferon (IFN)-α, -γ, and various chemokines such as IL-8, regulation-upon-activation normal T expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, MIP-1β are involved in progression of inflammatory events (21,22). Anti-inflammatory cytokines e.g., IL-4, -5, -10, -13 generally counteract the cellular activation and production of proinflammatory cytokines and involved in immunity and allergic reactions (2, 8). Chemokines are low-molecular weight cytokines that can mediate migration of leukocytes during inflammation for example CXCR1, CXCR2, CCR2 and CCR3 regulate leukocyte trafficking to tissue sites of inflammation (23, 24).

Inflammation can be acute and limiting or chronic. The latter may be due to a persistent antigen resulting in conditions such as rheumatoid arthritis. Acute inflammation may lead to a systemic reaction known as the acute phase response in which stimulated macrophages secrete TNF-α, IL-1 and IL-6 which act on the hypothalamus to produce fever and on the liver to induce production of acute phase proteins (e.g., α_1-acid glycoproteins and CRP) by hepatocytes (25). In addition, TNF-α acts on vascular endothelial cells and macrophages to increase secretion of colony stimulating factors (e.g., macrophage-colony stimulating factor) that stimulate hematopoiesis resulting in increased white blood cells to fight infection and immune cells such as activated macrophages to secrete hydrolytic enzymes and reactive nitrogen products (26). Nitric oxide (NO) is a soluble gas that participates in normal physiological processes such as vasodilation and neurotransmission; however, overexpression may result in disease as observed in asthma, cardiovascular disorders and organ transplant rejection (27-29). NO is generated from L-arginine which is catalyzed by a group of enzymes called nitric oxide synthases (NOS): constitutive forms [endothelial NOS (eNOS), neuronal NOS (nNOS)] and inducible NOS (iNOS)] (30). Toxicity emerges when excessive concentration of NO is expressed. Alterations in constitutive forms (e.g., eNOS) may also cause disease (31). Unlike constitutive forms, iNOS activity is induced by proinflammatory cytokines (e.g., IFN-γ, IL-1β and TNF-α) and participates in events that lead to inflammatory disorders (18, 26, 32). Research in the area of inflammatory mediator overexpression (e.g., cytokines, NO) has been evolved from discovering and cataloging to determining roles in disease (33).

We have highlighted the therapeutic significance of altered inflammatory mediators in a review article published in 2001 (12). Since then, however, the interest on the topic has greatly increased as reflected in the body of the published reports. Hence, the intention of this review article is to update the readership with the most recent advances in the field.

INFLAMMATORY MEDIATORS AND PATHOGENESIS OF DISEASE

Acquired immunodeficiency disorder (AIDS), asthma, atherosclerosis, cancer, congestive heart failure (CHF), diabetes, rheumatoid arthritis and depression are examples of disorders in which disease pathogenesis has been linked to increased expression of proinflammatory mediators (17,21,34-44). In fact, inflammatory diseases are a major cause of mortality, in the year 2000 diseases of the heart, malignant neoplasms and diabetes accounted for over one-half of all deaths reported to the Centers for Disease Control and Prevention (45).

Overexpression of proinflammatory cytokines has also been associated with allograft rejection (46). For example, IFN-γ, sIL-2 receptor, IL-4 and IL-10 serum concentrations were compared in 105 infants and children after liver transplantation with and without acute graft rejection episodes. The incidence of acute rejection by age groups was 0-12 months (26.8%), 1 to 3 years (40%) and children greater than 3 years old (71.8%). There was significantly lower incidence of acute rejection episodes in infants up to 12 months of age compared to those greater than 1 year old. Analysis of serum Th1 and cytokine expression up to 24 months from children with and without rejection episodes is shown in Figure 1. Between the two groups, increased expression of IFN-γ and sIL-2 receptor was associated with acute rejection episodes. Except four weeks post-transplantation, cytokine patterns did not differ significantly from preoperative values in both

groups. Compared to healthy controls, patients with and without acute rejection 12 months post-transplantation showed no differences regarding the absolute number of T and B cells, T helper cells, cytotoxic T cells and activated (HLA-DR+) T cells, thus, differences between the two groups was not due to changes in populations of B- and T-cells. Increased Th2 expression i.e., anti-inflammatory cytokines IL-10 and IL-4 of infancy was concluded to be an important factor in reducing acute rejection episodes (46). Disorders that have been associated with proinflammatory mediator overexpression are shown in Table 1.

Disease due to overexpression of mediators of inflammation may also result from cytokine treatment or concurrent disorder. For example, patients afflicted with renal cell carcinoma, melanoma or hepatitis C virus infection, and administered IL-2 or IFN-α2b have been reported to experience depressive symptoms (185-187). In addition, rheumatoid arthritis is reported to be an independent risk factor for occurrence of cardiovascular disease (188,189). Cachexia, a wasting syndrome characterized by loss of fat tissue, skeletal muscle, bone tissue and anorexia, is another example of a disorder that may occur with other inflammatory diseases. This wasting syndrome is characterized by proinflammatory mediator overexpression (e.g., TNF-α) and contributes to mortality (190,191). Increased expression of proinflammatory mediators and wasting has been reported for patients afflicted with CHF, cystic fibrosis, tuberculosis and cancer (118,119,192-196). A prospective study that was conducted in which the frequency and prognostic importance of cachexia in patients with CHF was determined (120). Anker et al assessed 171 consecutive patients afflicted with CHF and discovered that 28 of these patients were cachectic. Compared to non-cachectic patients these individuals were slightly older, had reduced exercise capacity and time. They also had lower sodium plasma concentrations. Their left ventricular ejection fraction was, however, similar in both groups of patients. An 18-month follow-up of these patients was conducted in which all-cause mortality was the endpoint. The cachectic state was predictive of mortality at 18 months independent of age, CHF classification, left ventricular ejection fraction, peak oxygen consumption and sodium levels. Congestive heart failure patients who had two risk factors such as reduced oxygen consumption (less than 14 ml/min/kg) and cachexia had an extremely poor survival compared to patients that did not have these two risk factors. Mortality in CHF patients with cachexia was very high: 18% at 3 months, 29% at 6 months and 50% at 18 months compared to those without cachexia as shown in Figure 2.

Similarly, in cancer patients the altered balance between proinflammatory and anti-inflammatory cytokines is considered a major determinant of progression to cancer cachexia and reported to account for almost one-third of cancer deaths (190,191,196). Normalizing inflammatory responses in cachectic patients may help to increase the effectiveness of various treatments. For example, modifying proinflammatory cytokine concentrations may improve the effectiveness of administered nutrients in total parenteral nutrition, which may be of benefit to those receiving parenteral nutrition afflicted with cachexia (197).

Altered proinflammatory mediator expression occurs with aging. Increased concentrations of IL-6 in older persons are linked to development of depression and atherosclerosis. In fact, overexpression of IL-6 and CRP in elderly individuals has been associated with disease, disability and mortality (92,93,198,199). To investigate whether TNF-α overexpression is associated with cognitive function, atherosclerosis and general healthy status, serum concentrations of TNF-α, sTNFRII (free and bound), IL-6 and CRP have been determined in 126 centenarians, 45 (81 year-old), 23 (55-65 year-old) and 38 (18-30 year-old) individuals (91). Concentrations of TNF-α and TFNRII were greatest in centenarians and greater in 80 year-olds compared to younger groups. Concentrations of IL-6 were greater in 55-65 year-old, 80 year-old and centenarians than younger people. High TNF-α concentrations were associated with moderate to severe dementia independent of atherosclerosis and Alzheimer's disease. Increased concentrations of TNF-α were correlated with IL-6, sTNFRII and CRP in the centenarians showing that increased concentrations of inflammatory mediators observed in aged individual is associated with development of a persistent low-grade inflammatory state.

Overexpression of proinflammatory mediators in disease is reported to be linked to treatment failure. For example, increasing levels of IL-1ra and IL-6 during the first 2 days of hospitalization in unstable angina patients have been shown to be associated with increased risk of in-hospital coronary events (200).

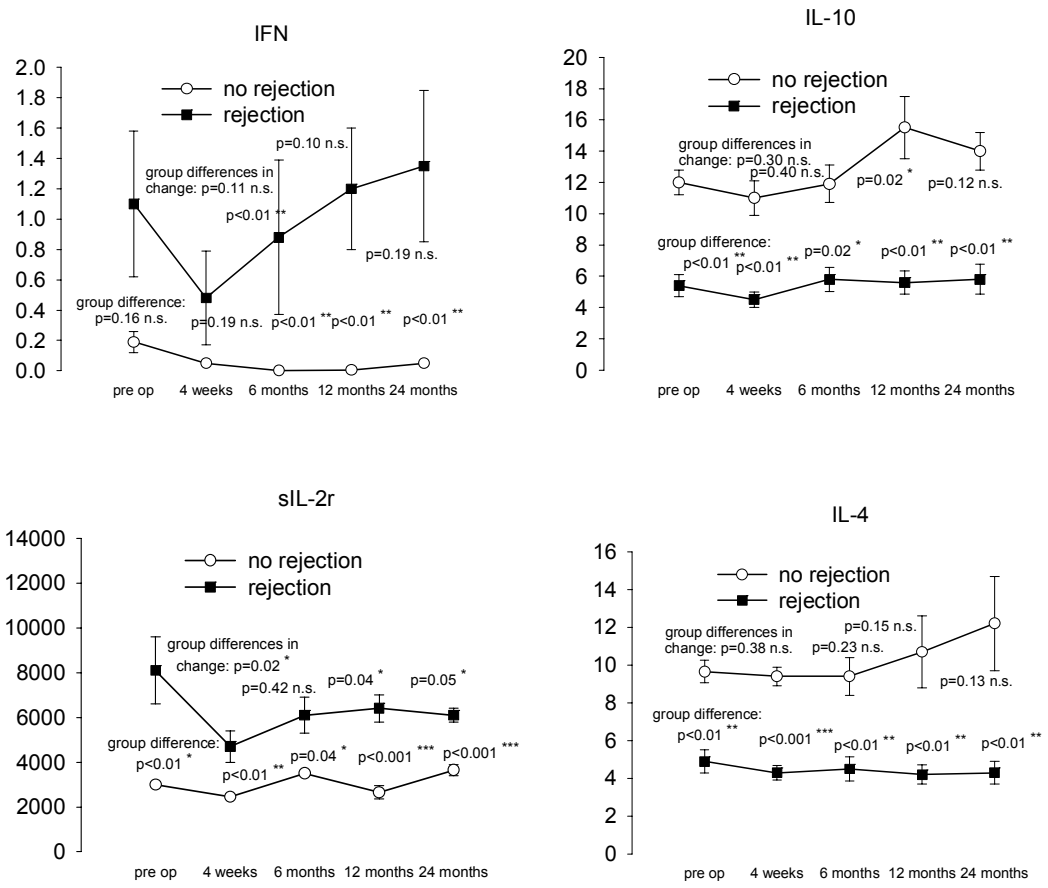

Figure 1. Relationship between proinflammatory mediator overexpression and acute liver rejection episodes. No differences were found within each group (no rejection versus rejection), however, patients experiencing acute rejection episodes had increased concentrations of proinflammatory cytokines/receptors (Th1) and decreased concentrations of anti-inflammatory (Th2) cytokines [mean cytokine/receptor concentration (pg/ml) versus pre- and post-operative transplantation, (n=11/Group)]. From reference 46 with permission.

In further support, to determine whether the proinflammatory state independently determines outcome in patients with unstable angina, inflammatory markers were compared between 135 stabilized and 76 refractory patients. Standard medical therapy consisted of acetylsalicylic acid (ASA), nitroglycerine, heparin, β-adrenergic blockers and calcium channel blockers.

Refractory patients had higher serum concentrations of CRP, fibrinogen and erythrocyte sedimentation rate compared to stabilized patients, which was not affected by presence or absence of myocardial necrosis (measured by troponin-T), or interval between onset of angina and blood collection. In severe unstable angina, the proinflammatory state was determined to be the main independent determinant for short term therapy failure (201).

CRP overexpression has been associated with many cardiovascular disorders and suggested to be predictive of treatment failure (202-205). In fact, CRP and the high-sensitivity CRP (hs-CRP) assays have provided benefit in determining relationships between the mediator overexpression and disease, effectiveness of pharmacotherapy, and outcome (206-209). Immunmodulatory effects of CRP in inflammatory disorders reported to date are upregulation of adhesion molecules, monocyte recruitment, and complement activation, interaction with lipids and thrombosis, and inhibiting NO production (74,210).

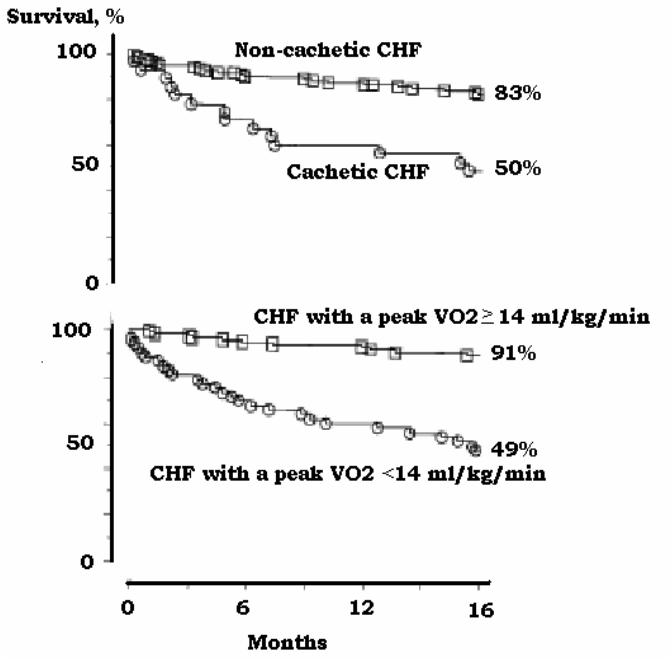

Figure 2. Kaplan-Meier survival curves showing mortality of cachetic patients with congestive heart failure (CHF). Mortality of cachetic patients with CHF was similar to those that had low peak oxygen consumption (<14 ml/kg/min). Survival in ambulatory patients with congestive heart failure (top frame) with (n=28) and without (n=143) cardiac cachexia and (bottom frame) survival in these patients based on VO_2 (oxygen consumption) with peak VO_2<14 (n=53) and VO_2>14 ml/kg/min (n=118). From reference 120 with permission.

Post-myocardial infarction patients with high CRP concentrations are more likely to have a history of unstable angina and symptom onset at lower levels of activity than those with lower concentrations emphasizing the role of CRP in disease progression (211,212). Pietila et al studied the relationship between serum CRP and mortality in patients who had experienced an acute myocardial infarction (213). CRP concentrations and creatine kinase and its MB isozyme were measured in 188 patients who had undergone an acute myocardial infarction. CRP concentrations were measured daily for 6 days after the infarction, serum creatine kinase and its MB isozyme were measured on admission and twice daily for 3 days. Mortality was determined at 3, 6, 12 and 24 months after the infarction and compared with CRP and creatine kinase values. Peak serum values of creatine kinase and its MB isozyme were similar in all patients and were not associated with mortality. On the other hand, increased concentrations of CRP in patients the first 2 days after an acute myocardial infarction were associated with increased risk of dying of cardiac failure or sudden death 6 months after the infarction as shown in Figure 3.

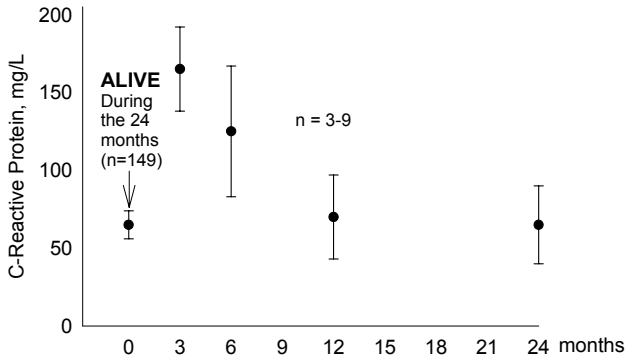

Figure 3. Relationship between CRP serum concentrations measured 2-4 days after myocardial infarction and mortality. From reference 213 with permission.

In addition, elevated CRP concentrations in patients at discharge are reported to be associated with recurrent instability in patients with unstable angina independent of coronary revascularization procedure (214). Increased CRP concentrations are also associated with cardiovascular risk factors in the elderly and predictive of overall and cardiovascular mortality (93,215-217). Similarly, measurements of TNF-α soluble receptors were associated with older age and increased levels of CRP that predicted treatment outcome in patients with Hodgkin's disease and non-Hodgkin's lymphoma (218). Increased inflammatory mediator expression and altered pharmacological response for various disorders are listed in Table 2.

INFLAMMATION AND PHARMACO-KINETIC/ PHARMACODYNAMICS RELATIONSHIPS

Inflammatory conditions and inflammation-induced pathophysiological changes have been associated with increased plasma concentrations of some important drugs (249-251). Probable explanations for increased drug concentration are greater protein binding due to increases in α_1-acid glycoproteins during the acute phase response and reduced metabolism due to NO and its breakdown products inactivating cytochrome P450 isozymes. (252-255). Contributions of increased protein binding and reduced metabolism depends on the role of

metabolism and protein binding (251,256,257). Drugs that are highly protein bound and undergo extensive first pass metabolism are targets for inflammation-induced changes in pharmacokinetics. Substantial increases in plasma concentrations of propranolol, a highly protein bound and efficiently metabolized drug, are reported for patients afflicted with various inflammatory disorders (249).

Similarly, increased concentrations of verapamil enantiomers have been reported in patients with rheumatoid arthritis as shown in Figure 4 (230). This was accompanied by elevated IL-6 and serum nitrite (stable breakdown product of NO) concentrations compared to healthy volunteers. Verapamil similar to propranolol is highly protein bound and undergoes extensive first-pass metabolism thus elevated plasma concentrations were attributed to changes in both protein binding and hepatic metabolism. One would anticipate that higher concentration of verapamil in arthritic patients would result in increased activity. Quite the contrary, however, the observed elevated total and plasma unbound verapamil concentrations in arthritic patients were accompanied by a decreased dromotropic (L-type cardiac calcium cardiac channel) response demonstrated by a reduced prolongation of the cardiac PR interval as shown in Figure 4.

In support, data generated from elderly patients also demonstrate a reduced dromotropic activity of verapamil despite increased plasma concentrations (234). Furthermore, in elderly individuals β-blocker therapy does to appear to reduce risk of stroke or coronary events (236). In fact, β-blocker therapy is reported to be not efficacious as the first line therapy in hypertensive elderly patients (237). A reduced β-adrenergic responsiveness to propranolol in the presence of increased plasma concentrations using an animal model of inflammation has been observed (257). Plausible explanations for the reduced potency of verapamil in arthritic patients and propranolol in inflamed rat include increased protein binding of drug and/or altered function of L-type cardiac calcium channels and β-adrenergic receptors, respectively. Proinflammatory mediators have been shown *in vitro* to reduce activity of β-adrenergic, cardiac calcium and potassium channel receptor function due to down-regulation and/or inactivation of receptors and channels (258-263).

Reduced response to β-adrenergic antagonist has also been reported in the absence of pharmacokinetic alteration. Sotalol is a β-adrenergic as well as potassium channel blocker. It is negligibly protein bound, and undergoes little or no hepatic clearance. Inflammation, therefore, does not influence sotalol pharmacokinetics. Nevertheless, both β-adrenergic and cardiac potassium channel blocking activity of sotalol are reduced in the rat model of inflammation (264).

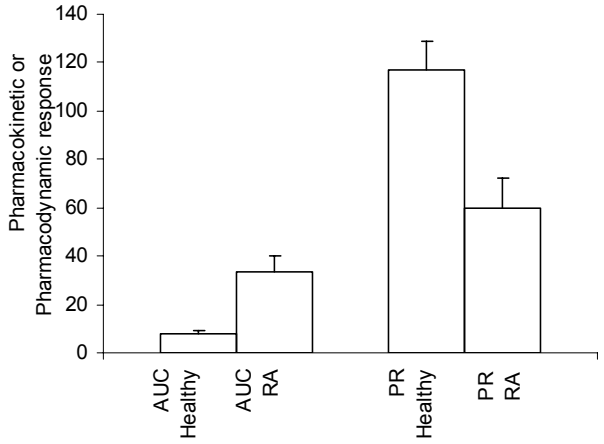

Figure 4. Area under serum S-verapamil concentration-time curves (AUC, mg/L^{-1} • min) and the area under percent PR prolongation (from baseline, %Xh) following 80 mg of racemic verapamil to healthy volunteers and rheumatoid arthritic patients (RA). Error bars represent standard error of the mean (n=8/group). From reference 230 with permission.

The reduced response appears to be reversed with administration of anti-TNF-α monoclonal antibody, which is associated with reduced serum concentrations of TNF-α and nitrite. Similar observations have been made for atenolol (265) and propranolol (266). Interestingly, a recent report indicates that RA patients who are treated with anti-TNF-α antibodies demonstrate a lower incidence of first cardiovascular events (267). It should be noted that the use of anti-TNF therapy may also result in serious adverse effect. Although preclinical and preliminary clinical data suggested that they may favorably modify the course of disease, their use in New York Heart Association class III and IV heart failure and left ventricular ejection fraction may, indeed, adversely affected the clinical condition of patients with moderate-to-severe chronic heart failure particularly in high doses (268).

The reduced dromotropic activity of β-adrenergic, calcium channel and potassium channel antagonists appear to be associated with increased expression of proinflammatory mediators, and independent of pharmacokinetic alterations. The available evidence points to reduced binding of the

drugs to the target proteins at the receptor level as shown in Figure 5 (269). The reduction in binding may be attributed to gene downregulation resulting in reduced mRNA synthesis or posttranslational alteration of receptor. Not all cardiovascular receptors are down-regulated by inflammation. At least for the angiotensin II type 1 receptors (AT_1R) antagonist, valsartan, rheumatoid arthritis appears to have no down-regulating effect. Indeed, a trend toward an up-regulation is evident (270). This does not appear to be pharmacokinetic-dependent. A probable explanation for the trend towards increased potency may be upregulation of AT_1Rs in inflammatory conditions due to the anti-inflammatory nature, and effect on the Th1 cells of this class of drugs (11,271-274). Indeed, angiotensin by itself has been identified as an endogenous compound with inflammatory properties (11). This may make AT_1R antagonists as cardiovascular drugs of choice in the treatment of patients with inflammatory diseases.

CONCLUSION

Altered pharmacokinetics and/or pharmacodynamics have been reported for many drugs including some used to treat cardiovascular diseases, asthma, cancer, diabetes and depression. In addition, conditions such as old age and obesity appear to be associated with alteration of action and disposition of some drugs. All these are associated with altered inflammatory mediators. Whether this association is causative or incidental is, at most, controversial and remains to be unequivocally understood. Nevertheless, altered concentration of inflammatory mediators appears to influence pharmacokinetic-pharmacodynamic relationships. This may render the conventional drug effect vs. concentration and/or dose-response relationships more complicated as the mediators' concentrations may have to be considered in the equation. Hence, equations describing effect-concentration relationships may have to be expanded from the present two dimensional to multidimensional ones. For example, monitoring of inflammatory mediators in cancer patients has been suggested to identify patients with very poor benefit-risk ratios for drug treatment due to the association of inflammation with cancer, altered drug metabolism, and reduced response to chemotherapy (275). Changes in drug response are especially relevant to the elderly who have increased incidence of concurrent conditions in conjunction with proinflammatory mediator overexpression that occurs with aging. In fact, depressive symptoms in elderly individuals are reported to constitute an independent risk factor for development of coronary heart disease and mortality (276). Understanding the influences of proinflammatory mediator overexpression on drug disposition and activity, therefore, may help to explain variability in response to pharmacotherapy.

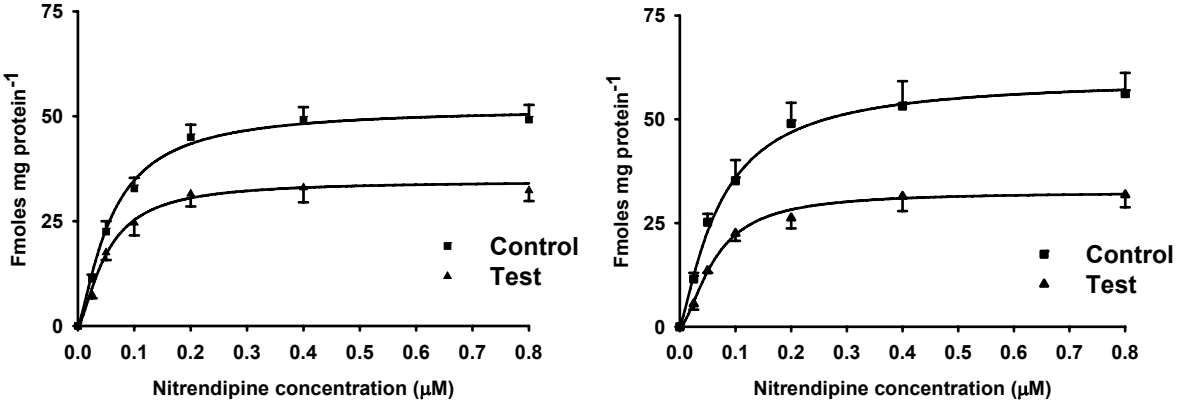

Figure 5. Binding of ^{3}H-nitrendipine to cardiac cell membranes of rats with acute (left) and chronic (right) inflammation. Binding (B_{max}) was reduced in rats with inflammation compared to controls (acute: control, 63.2±2.5; interferon treated, 46.4±2.0; chronic: control, 66.8±2.2, adjuvant treated, 42.2±2.0 fmolmg-1 protein). In chronic inflammation increase in dissociation constant (K_D) compared to normal rats was observed (normal, 0.09±0.01; treated, 0.14±0.02 μM). From Reference 269 with permission.

Table 1: Proinflammatory mediator overexpression and disease

Disorder	Inflammatory Mediator Expression
Acquired Immunodeficiency Syndrome (AIDS)	Increased secretion of TNF-α, IL-1 and IL-6 by macrophages and monocytes correlated with viral load and polymorphisms in chemokine receptor and gene expression is suggested to be associated with disease susceptibility and progression (47, 48); increased capacity of dendritic cells exposed to HIV-1 to produce TNF-α and IL-1β (47, 48); upregulation of CCR5 chemokine receptor (21, 47-49); IL-10 overexpression contributes to B-cell hyperactivity and risk of AIDS-lymphoma (50).
Acute Infection	Elevated myeloperoxidase and IL-6 in severe infections served as a distinction between viral and bacterial causes (51).
Atopic Diseases	Promotion of eosinophilia and cytokines that regulate IgE in atopic diseases including asthma, allergic rhinitis and atopic dermatitis (52,53); allergic states and IL-4, IL-5, IL-10 and IL-13 were associated via Th2 responses (53,54); administration of IL-12, IFN-α/γ are suggested to alleviate atopic disease (53,55); increased NO in exhaled air reflected airway inflammation in asthma patients (56); increased IL-5 concentrations with subsequent eosinophil activation was involved with pathogenesis of asthma, IL-5-activated eosinophils downregulate IL-5 membrane receptor and release soluble IL-5 receptor blunting subsequent IL-5-dependent inflammatory events complicating treatment (57).
Behçet's Syndrome	Active disease was associated with increased IL-6, -10, -17, -18 and IFN-γ compared to remission (58).
Cancer	Increases IL-6 and IL-6sR are associated with progression and metastasis of prostate cancer (59); elevated serum levels of IL-6 and sIL-6 receptor correlated with lower life expectancy in patients with multiple myeloma (60); increased IL-17 concentrations promoted angiogenesis and tumor growth (61).
Cardiovascular Disorders	
Acute myocardial infarction	Elevated plasma IL-6 levels after acute myocardial infarction (62); CRP localizes in infarcted heart tissue (63); sequential appearance of IL-1β and IL-6 in plasma of patients that experience an acute myocardial infarction (64); TNF-α overexpression post-myocardial infarction is not confined to the infarct or peri-infact zone but is also present in the tissue contralateral to the infarct (65); increased serum CRP concentrations predicted MI in patients with peripheral vascular disease severe enough to require revascularization (66); high CRP levels prior to thrombolysis was associated with reperfusion failure with unfavorable short and long term prognosis (67).
Atherosclerosis	CRP is a strong predictor for future coronary events in healthy individuals (68); increased endothelium concentrations of IL-1 and TNF-inducible adhesion molecules P-selectin, E-selectin, VCAM-1 and intracellular adhesion molecule (ICAM)-1 in atherosclerotic tissue (69,70); high density lipoproteins may protect against coronary artery disease by inhibition of adhesion molecules (71); high density lipoproteins are suggest to inhibit TNF-α and IL-1β from increasing expression of E-selectin, VCAM-1 and ICAM-1 (36,69); endothelial dysfunction is associated with altered NO bioavailability due to either reduced formation or accelerated degradation (72); CRP levels predicted future risk of coronary heart disease in healthy middle-aged men (73);CRP suggested to have a fundamental role in atherogenesis (74).
Congestive Heart Failure	Increased concentrations of TNF-α and IL-6 were associated with progression from asymptomatic to symptomatic left ventricular dysfunction and excessive TNF-α levels associated with mortality (38,75,76); IL-6 is a strong predictor of disease progression (77); patients without cachexia that experience acute decompensation have increased levels of TNF-α (78).
Hypertension	Increased IL-1ra concentrations in essential hypertensive patients compared to normotensive individuals (79); hypertensive type II diabetic patients prothrombic state suggested to result in higher incidence of thrombotic events compared to non-diabetic hypertensive patients

	(80); hsCRP independent risk factor for hypertension (81).
Unstable angina	Imbalance between TNF-α and IL-10 reported for patients with unstable angina (82); increased concentrations of markers of inflammation in unstable angina (83); increased concentrations of CRP, macrophage colony-stimulating factor (MC-SF) and IL-6 was related to number of diseased vessels and reduced after six weeks of aspirin treatment (84); preprocedural CRP predicted early complications and restenosis after coronary angioplasty (85); higher levels of IL-10 were associated with reduced risk of coronary events in patients with unstable angina (86); increased IL-6 serum concentrations independent marker of increased mortality in patients with unstable coronary artery disease (87).
Stroke	Reduced IL-10 concentrations were associated with neurological worsening in patients that experienced ischemic stroke (88).
Elderly	Age associated changes in T-cell chemokine expression is suggested to contribute to poor clinical outcome of T-cell chemokine receptor-dependent diseases in the elderly (89); elevated concentrations of IL-1, TNF-α, IL-6 and sTNFRII (90,91); increased concentrations of TNF-α independent of atherosclerosis (91); elevated concentrations of IL-6 and CRP predicted disability onset (92); increased concentrations of CRP and IL-6 were associated with mortality (93); increased CRP concentrations in the elderly was associated with development of diabetes mellitus (94); after challenge with endotoxin aging was associated with more rapid increase in CRP and prolonged inflammatory response and fever compared to younger individuals (95); high levels of TNF-α were associated with high prevalence of atherosclerosis in 81-year-old individuals (96); elevated concentrations of TNF-α predicted mortality in centenarians (97); elevations in TNF-α and IL-6 were associated with mortality in 80-year-old people (98).
Fever	In periphery and brain increased concentrations of IL-1α, 1β, TNF-α and IL-6 (99); post-myocardial infarction patients with prolonged fever had increased inflammatory activity (100).
Gastrointestinal Disorders	
Crohn's Disease	High Th1 cell activity and increased proinflammatory state (101).
Peptic Ulcer	High ulcerogenic potential of Helicobacter pylori is linked, in part, to increased activity of IL-8 and TNF-α (102); Helicobacter pylori and NSAIDs cause ulcer recurrence through production of IL-1 and TNF-α by macrophages accumulated at the ulcer scar (103)
Liver Disease	Individuals afflicted with non-alcoholic steatohepatitis have increased TNF-α levels compared to healthy persons and plays a role in pathogenesis of disease (104); plasma levels of IL-18 and IL-18 binding protein are elevated in patients with chronic liver disease and correlate with severity of disease (105).
Neurological Diseases	
Alzheimer's Disease	Neuroinflammation due to inflammatory mediator overexpression is associated with behavioral disturbances (106); increased IL-1 expression in Alzheimer brain is directly related to plaque formation and progression and neuronal overexpression of acetylcholinesterase (107); TNF-α, IL-1β and IL-6 overexpression stimulated production of amyloid-β which is crucial for neurodegeneration in Alzheimer's patients (108,109).
Cerebral ischemia	Increased IL-1, TNF-α, TNF-β and IL-6 concentrations in patients that have experienced acute ischaemic brain injury (110,111); elevated IL-6 and TNF-β serum levels in acute stroke patients regardless of subtype (110); increased expression of TNF-α, IL-1 and ICAM-1 (111).
Down's Syndrome	Overexpression of IL-1 in middle-aged individuals that have concurrent Alzheimer-type changes and in young and fetal Down's patients (109).
Multiple Sclerosis	Elevated TNF-α concentrations in serum and cerebral spinal fluid (112,113); brain endothelium and astrocytes increased expression of ICAM-1 (114); increased concentrations of LFA-1, ICAM-1, FA-3 adhesion molecules and chemokines MCP-1, -2, -3, IP-10, GRO-α, RANTES, MIP-1α and -1β (110,115,116).

Nutritional Disease	Individuals undergoing long-term home parenteral nutrition without clinical evidence of infection had increased sTNF-RII and IL-6 concentrations indicating long-term home care total parenteral nutrition can be associated with persistent low-grade inflammatory state (117); increased TFN-α concentrations in congestive heart failure patients correlated independently with wasting (118-120); increased serum TNF-α levels in patients with gastrointestinal cancer correlated with severity of weight loss (121).
Obesity	Elevated plasma CRP concentrations (122); increased concentrations of TNF-α and soluble receptors in overweight individuals associated with insulin resistance (123,124); plasma TNF-α concentrations decreased with weight loss in obese individuals (125); elevated IL-6 concentrations decreased in serum and subcutaneous tissue of obese women after weight loss (126); elevated CRP, TNF-α and IL-6 concentrations have been linked to insulin resistance and endothelial dysfunction with obesity and cardiovascular disease (127); alterations in TNF-α gene locus involved with pathogenesis of obesity and obesity-associated hypertension (128); TNF-α system was associated with altered plasma leptin concentrations in obese individuals (129); increased IL-8 concentrations in obese individuals and related to fat mass and TNF-α system (130); adipose tissue releases mediators that influence body weight and inflammatory state (131); adipose tissue and development of inflammatory state contributing to obesity associated vasculopathy and cardiovascular disease (132).
Diabetes	Th-1 and Th-2 cells and their respective mediators participate and cooperate in inducing and sustaining pancreatic islet cell β-cell destruction in insulin dependent diabetes (133); inflammation important factor in pathogenesis of diabetes and metabolic disorders in women (134); increased CRP levels suggested to predict development of type 2 diabetes (135); obesity and diabetes inflammatory states in which mediators of inflammation contribute to insulin resistance (136).
Pain	Soluble TNF-α and IL-1 receptor antagonist administered intrathecally were additive in reducing mechanical allodynia (137); IL-6 pathway is associated with altered pain perception (138); hyperalgesia induced by TNF-α via stimulating release of IL-1 (139); hyperalgesia induced by peripheral inflammation is associated with IL-1 overexpression (140); spinal cord glia and glially derived proinflammatory cytokines suggested to be powerful modulators of pain (141); interleukin-1β mediated induction of cyclooxygenase-2 in neurons of the central nervous system contributes to inflammatory pain hypersensitivity (142); bradykinin B_2 receptors are suggested to be involved with the acute phase of the inflammatory and pain response (143); TNF-α expression is suggested to be upregulated in Schwann cells influencing central pain processing in painful neuropathies (144).
Pancreatitis	Matrix metalloprotinase-1, tissue inhibitor of metalloprotinase-1 and TNF-α levels were higher in non-survivors than survivors of acute pancreatitis (145); inflammatory mediators TNF-α, IL-1β, IL-6, IL-8, PAF, IL-10, C5a, ICAM-1 and substance P have a critical role in progression of acute pancreatitis (146).
Parasitic Infections	Increased TNF-α concentrations in patients with Plasmodium falciparum malaria is associated with pathogenesis of disease (147).
Psychiatric Disorders	
Delerium	Increased concentrations of interferons and interleukins during stress, rapid growth, inflammation, tumor, trauma and infection and administration of interferons and interleukins are reported to be associated with delerium (148).
Dementia	Increased IFN-α and decreased TGFβ-1 were related to progression of AIDS dementia complex and has been correlated with excessive neurocognitive dysfunction (149,150).
Depression	Increased expression of IL-1β, IL-6 and IFN-γ, IL-1ra, sIL-6r and TNF-α (151,152); increased IL-1β concentrations in cerebrospinal fluid (152); increased concentrations of IL-6, sIL-6r, sIL-2r and transferrin receptor in major depression (44).
Dysthymia	Increased production of IL-1β (153).
Obsessive Compulsive	Decreased plasma concentrations of IL-1β and TNF-α (154); decreased TNF-α but

Disorder	increased cortisol concentrations (155).
Schizophrenia	Increased concentrations of IL-6 and TNF-α (156-158); increased IL-1β polymorphism (159); drug-naïve schizophernic patients had increased IL-2 and IFN-γ production compared to controls (160).
Sleep disorders	TNF-α and IL-6 suggested to play an important role in mediating sleepiness and fatigue in disorders of excessive daytime sleepiness (161); systemic inflammatory response and reduced plasma availability of tryptophan was related to primary sleep disorders and major depression (162).
Stress	Psychological stress is associated with increased production of TNF-α, IL-1, IL-1ra, IFN-γ and lower production of IL-4 and IL-10 (163); increased expression of neutrophils, monocytes, $CD8^+$, $CD2^+CD26^+$ and $CD2^+HLA\text{-}DR^+$ T cells and $CD19^+$ B cells (164); post traumatic stress disorder was associated with increased IL-6 signaling (165).
Rheumatoid Arthritis	Increased concentrations of TNF-α as a central proinflammatory mediator (16,17) increased concentrations of IL-1, IL-6, TNF-α, GM-CSF, and chemokines IL-8, RANTES, GRO-α, MIP-1α, MIP-1β, MCP-1 (16,17,166,167).
Sepsis	Systemic inflammatory response syndrome due to pro-inflammatory mediator excess is associated with severe inflammatory responses then excessive anti-inflammatory responses possibly leading to increased susceptibility to infection (168-170); septic shock is caused at least in part by excessive or dysregulated host inflammatory responses (171).
Thyrotoxicosis	Increased concentrations of IL-6 and IL-8 in patients afflicted with thyrotoxicosis with levels decreasing as patients become euthyroid on antithyroid treatment (172).
Transplantation	
Heart	Increased concentrations of TNF-α and IL-6 in myocardium of malfunctioning donor hearts (173); association between increased IL-6 receptor concentrations and acute cardiac allograft dysfunction in the early perioperative period (174); pathological link between hypertension and increased NO production, decreased asymmetric dimethylarginine levels, and TNF-α activation (175); lipid mediators of inflammation implicated in allograft rejection (176).
Liver	TNF-α polymorphism associated with increased production associated with acute hepatocellular rejection (177); Th2 cytokine production is associated with improved graft acceptance in infants after liver transplantation (46); increased IL-8, IL-10 and TNF-α in during first post-operative week patients developed serious complications within the first month after surgery (178).
Lung	Increased expression of IL-1ra was associated with development of bronchiolitis obliterans syndrome a major limitation to survival (179).
Kidney	High IFN-γ production influenced acute rejection of kidney transplant (180).
Tuberculosis	Serum concentrations of sTNFRI and II and IL-1ra may serve as markers of disease activity (181); tuberculosis osteomyelitis is associated with elevated IL-6 concentrations (182).
Injury	
Burn	Increased IL-1 and IL-1β concentrations in burn patients and IL-6 concentrations were greater in those that died of their burn injuries compared to survivors (183).
Trauma	Peak levels of sICAM-1, sVCAM-1 correlated with disseminated intravascular coagulation and sustained inflammation caused by neutrophil endothelium interaction gave rise to multiple organ dysfunction syndrome resulting in poor patient outcome (184).

Table 2: Increased inflammatory mediator expression and pharmacological response

Disease	Pharmacological Response
Acquired Immunodeficiency Syndrome (AIDS)	African patients with AIDS exhibit greater TNF-α concentrations that may be responsible for reduced response to pharmacotherapy for tuberculosis HIV-1 load (219); persistent TNF-α activation is involved in highly active antiretroviral therapy failure (220); decrease in T-cells producing TNF-α and IL-4 are suggested to be early predictors of early response to and early failure of highly active antiretroviral therapy (221).
Atopic Disease	Glucocortocosteroid non-responsive bronchial hyper-responsiveness in mild asthma is associated with overproduction of IL-5 by lymphocytes (222); reduction in serum IL-5 was associated with resolution of atopic dermatitis (223); IL-6 overexpression is involved with pathogenesis of severe acute urticaria that is resistant to antihistamine treatment (224).
Cancer	Induction of doxorubicin resistance was associated with increased intracellular levels of TNF-α (225); increased concentrations of TGF-β are associated with resistance of prostate carcinoma to cytotoxic cancer therapy (226); resistance to tamoxifen in human breast carcinoma is linked to overexpression of TGF-β2 (227); increased IL-6 concentrations was related to insulin resistance in cancer patients (228); effectiveness of cyclophosphamide is suggested to be due to a pattern shift of cytokines from Th2 to Th1 around the tumor lesion (229).
Cardiovascular Disorders	
Acute myocardial infarction	Increase mortality after acute myocardial infarction is associated with overexpression of CRP independent of coronary revascularization procedures performed and medical therapy (214).
Arrhythmia	Reduced PR interval response to verapamil in rheumatoid arthritic patients (230).
Unstable angina	Greater CRP, fibrinogen and erythrocyte sedimentation rate in patients with refractory angina as compared to those stabilized (201); complicated hospital course linked with increased IL-1ra and IL-6 concentrations and an uneventful course when IL-1ra and IL-6 concentrations decreased 48 hours post-admission (200).
Hyperlipidemia	Reduced CRP levels in survivors of myocardial infarction when under therapy with hypolipidemic drug pravastatin which was independent of the magnitude of lipid alterations (231); statins are suggested to modulate immune responses by inhibiting induction of MHC-II expression by IFN-γ thus acting as suppressors of MHC-II mediated T-cell activation (232); lowering CRP with statins associated with better clinical outcome (207).
Diabetes	Overexpression of TNF-α in human muscle tissue was associated with insulin resistance (233).
Elderly	Reduced sensitivity of L-type calcium channels (234,235); hypertensive patients that received a β-blocker had no benefit of reduced coronary events (236); β-blocker not efficacious as first line therapy in hypertensive elderly patients (237).
Infectious Diseases	High levels of inflammatory cytokines are associated with poor clinical response to steroid treatment also recurrent episodes in leprosy patients (238); reduced myocardial responsiveness in septic shock patients suggested to be due to reduced β-adrenergic receptor function (239); increased plasma TNF-α plasma levels were associated with patient deterioration early in treatment of severe tuberculosis (240).
Obesity	Reduced sensitivity to verapamil in overweight individuals (241).
Pain	Chemotactic activities of μ- and δ-opioid receptors are desensitized following activation of chemokine receptors suggesting that activation of proinflammatory chemokine receptor downregulates analgesic function of opioid receptors enhancing pain perceptions (242).
Psychiatric conditions	
Depression	Increased IL-6 concentrations were associated with treatment failure (243).

Schizophrenia	Increased IL-6 concentrations were associated with refractory disease (244); successful antipsychotic therapy was associated with reduction in inflammatory state and normalization of immune responses (245,246).
Rheumatoid Arthritis	Restoring Th1/Th2 cell balance reverses treatment-refractory arthritis (247); resistance to disease-modifying drugs was associated with increased Th1 cells expressing p-glycoproteins (248).

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