C-Reactive Protein: Predicting Heart Attacks and Strokes

Olesya Litovka

Writer's Comment: Cardiovascular research in the past two decades has revealed older age, smoking, diabetes, obesity and hypertension strongly contribute to the risk of developing heart disease and cardiovascular problems. However, some of us may have friends and family members who suffer from heart disease while displaying few of the traditional risk factors. C-reactive protein has offered a novel prognostic tool for cardiovascular risk assessment independent of other co-factors. I decided to examine current applications and prospective utilization of C-reactive protein after beginning an internship for Dr. Ezra Amsterdam and Dr. Deborah Diercks of the UCDMC Department of Internal and Emergency Medicine. Dr. Amsterdam and Dr. Diercks are currently investigating whether CRP can help evaluate chest-pain patients at risk of developing a cardiovascular event in the ensuing 30 days after presenting to the emergency department with acute coronary syndrome. The goal of this paper was to explore CRP's prognostic value in predicting risk of major cardiac events and its usefulness in identifying high-risk individuals as an adjunct to lipid screening and cardiac risk scores.

—Olesya Litovka

Instructor's Comment: Olesya was a real sleeper. But not in the usual sense that "a.m." students have discovered, or so it seems, a radical cure for insomnia in the Americas and beyond. Oh, no. Olesya was a sleeper in the best possible sense of the word: a student who, as a member of my UWP 104F (Writing in the Health Sciences) class often went unnoticed—for the first weeks, at least—because she just went about her business with a profound sense of quiet assurance. And then her first assignment landed on my desk and I knew that Olesya P. Litovka was a force to be reckoned with. As James Joyce would put it, here was someone who could write in mean but forever elegant narrative forms—à la Joyce, in a spirit of "scrupulous meanness." Olesya's inclusion as a winning author in this year's *Prized Writing* with her distinguished piece, "C-Reactive Protein: Predicting Heart Attacks and Strokes," therefore does nothing more than speak volumes . . . makes the reader wake up and take stock of what the best science writers at UCD have to offer.

—James McElroy, University Writing Program

Introduction

Cardiovascular disease (CVD) is the number one killer of adults in the United States. An estimated 60 million Americans have some form of CVD, and approximately 1.5 million myocardial infarctions and 600,000 strokes occur every year.[1,2] Almost half of the individuals who suffer through heart disease related events die within a year of their initial episode.[2] Atherosclerosis inflammation is a principal cause of cardiovascular events and in the past decade the search for inflammatory biomarkers that could improve early detection of cardiovascular risks has gained momentum. Starting in 1994, cardiologist Paul M. Ridker and his colleagues at Harvard Medical School's Brigham and Women's Hospital pioneered research investigating C-reactive protein (CRP) as a prognostic CVD biomarker. Ridker's studies indicate baseline CRP levels in "apparently" healthy men and women predict future risks of heart attack, stroke, and sudden cardiac death.[1]

CRP, Atherosclerosis and CVD

C-reactive protein was discovered 70 years ago but its role in atherogenesis is still an open research topic.[1] Recent findings are reviewed in G.M. Hirschfield and M.B. Pepys's 2003 "C-reactive protein and cardiovascular disease: New insights from an old molecule." Hirschfield and Pepys explain that the human immune system naturally produces CRP in response to acute injury, infection, and tissue damage.[3] Baseline CRP concentrations are 35-40% heritable in healthy individuals, but following tissue necrosis CRP levels can elevate over 10,000-fold within 48 hours.[3] CRP is also deposited within the damaged tissue of all acute myocardial infarcts, and CRP plasma concentrations reflect necrosis extent in ischaemic myocardial injury.[3] Hirschfield and Pepys argue that the deposited CRP may activate plasma lipoproteins and initiate local inflammation, which is a major feature of atherosclerotic plaque formation and occurrence of atherothrombotic events.[3] CRP presence within myocardial lesions suggests it may also contribute to CVD pathogenesis.

James M. Backes's "Role of C-reactive protein in cardiovascular disease" further investigates inflammatory effects in coronary vessels. Published in the January 2004 issue of *The Annals*

of Pharmacotherapy, Backes's article explains that hypertension, diabetes, and obesity cause vascular endothelium injury and trigger macrophage release into the blood stream.[2] Macrophages oxidize and deposit low-density lipoprotein cholesterol (LDL-C) into blood vessels, where it serves as a building block for atherosclerotic plaque.[2] LDL-C collections form fatty streaks on vessel walls, leading to pro-inflammatory cytokine elicitation and increased hepatic CRP production.[2] CRP binds more LDL-C and facilitates macrophage phagocytosis of the lipoprotein, thus accelerating fatty streak formation.[2] Cholesterol build-up disrupts coronary and cerebrovascular circulation, causing arterial hardening, early atherogenesis and vessel lumen obstruction.[2] Progressive narrowing of blood vessels by atherosclerosis increases the risk of CVD-related stroke, heart attack, congestive heart failure, and sudden cardiac death.

High-Sensitivity CRP and Cardiovascular Risks:

CRP HAS a 19-hour plasma half-life, making it easy to measure with an inexpensive blood test that can be added to regular cholesterol screening.[1] CRP synthesis rate determines plasma concentrations, thus indicating the severity of pathological processes stimulating CRP production.[3] Circulating CRP values are more reflective of ongoing inflammation than traditional biochemical parameters including plasma viscosity and erythrocyte sedimentation rate.[3] Earlier CRP tests were crude and only detected elevated levels above 8 milligrams per liter (mg/L).[2] While these blood tests were able to diagnose severe inflammatory conditions, they did not indicate lower-grade inflammation seen in cardiovascular diseases. High sensitivity CRP (hs-CRP) assays were developed in the mid-1990s and allowed detection of CRP levels below 0.3 mg/L and within the cardiac range.[2] Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) endorsed the use of hs-CRP in January 2003 for patients with prior heart attack history and for those admitted with acute heart disease syndromes.[1]

The CDC and AHA issued the first clinical guidelines suggesting hs-CRP levels of 1 mg/L, 1 to 3 mg/L, and above 3 mg/L be used to represent low, moderate, and high cardiovascular risks respectively.[4] CRP levels are similar in men and women, and the average middle-aged American has a 1.5 mg/L reading.[1] Over 25% of

the U.S. population has a level greater than 3 mg/L and current hs-CRP use is in primary prevention and detection of high-risk individuals not yet known to have a problem.[1] Ridker's 2003 "C-reactive protein" claims that even though CRP testing is not mandatory, it may improve an intermediate-risk individual's overall prognostic estimate.[1] Ridker's research suggests elevated CRP levels predict subsequent risks for 30-40 years, allowing ample time to institute lifestyle changes and pharmacological intervention to prevent "first ever" heart attack and stroke.[1]

Clinical and Cohort Studies

Men and CRP values

The standardization of hs-CRP assays allowed Ridker and his colleagues to investigate CRP's predictive abilities for future vascular events. They conducted the first Physician's Health Study (PHS) in 1996-1997 on 1,086 healthy men with no previous cardiovascular events including myocardial infarction (MI), stroke, or peripheral arterial disease.[5] The study measured CRP as a marker for systemic inflammation and investigated whether plasma CRP concentrations were higher among men who experienced a cardiovascular event over an 8-year follow up.[5] PHS observed 543 men who had a subsequent MI, stroke, or venous thrombosis in relation to 543 men with no ensuing symptoms.[5] Ridker found baseline plasma hs-CRP concentrations were higher in men who had a MI (1.51 mg/L vs. 1.31 mg/L) or stroke (1.38 mg/L vs. 1.13 mg/L) than among men without vascular events.[5] His data also indicated men in the highest CRP quartile (above 2.11 mg/L) had three times the relative risk (RR) of MI and two times the risk of ischemic stroke or peripheral vascular disease than men in the lowest quartile (below 0.55 mg/L).[5]

Ridker's PHS revealed that estimated cardiovascular RR remained stable for over 6 years after initial MI or stroke.[5] The RR was also independent of hypertension history, cholesterol levels, diabetes, and parental coronary heart disease (CHD) history.[5] Ridker's findings were consistent with the 1996 Multiple Risk Factor Intervention Trial (MRFIT) conducted on high-risk men with coronary risk factors including smoking, hyperlipidemia, and hypertension.[6] Lewis H. Kuller and colleagues of the University of Pittsburgh

Department of Epidemiology investigated 491 controls, 148 CHD deaths, and 98 MI cases.[6] Their results, published in the *American Journal of Epidemiology*, revealed that baseline hs-CRP levels correlated with future MI and CHD mortality during the 6-7 and 17-year follow-ups.[6] Approximately 66% of individuals who died had hs-CRP levels in the upper two quartiles and their RR was independent of confounding factors.[6] The MRFIT study demonstrated the first link between elevated hs-CRP and subsequent coronary heart disease mortality in healthy men.

Wolfgang Koenig's 1998 study results confirmed the prognostic relevance of CRP to the risk of CHD in a randomly selected cohort of initially healthy middle-aged men. Koenig and colleagues measured hs-CRP levels of 936 men who participated in Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg cohort between 1984 and 1995.[7] Participants were adjusted for age, smoking, hypertension and dyslipidemia.[7] Age, body mass index, and relative work activity were also assayed as potential confounders.[7] Data revealed a linear relationship between CRP and future risk of fatal or nonfatal coronary events. This relationship remained independent of diabetes, cholesterol, smoking, and hypertension.[7] Potential confounders only added a 5% change to the CRP-estimated RR.[7] Koenig's study suggests that low-grade inflammation is involved in atherosclerosis pathogenesis and that hs-CRP can enhance coronary risk assessment.

The recent 2002 Honolulu Heart Program (HHP) study further confirmed Ridker's previously established relationships between CRP and MI. Cited in Michael B. Clearfield's 2005 review, "C-reactive protein: A new risk assessment tool for cardiovascular disease," the HHP assessed CRP levels in clinically healthy men over a 20 year follow-up.[8] CRP levels were associated with coronary events that occurred up to 15 years later, and five years into the follow-up. MI risks correlated with increasing hs-CRP levels.[8] At 10-15 years into the follow up, MI risks were 2.1 times higher for men in the highest hs-CRP quartile versus those in the lowest quartile.[8] The strongest correlation between CRP and MI was seen in men without cholesterol, hypertension, or type 2 diabetes mellitus confounding risk factors.[8] HHP also found that ischemic stroke risk increased with higher hs-CRP levels in men over 55 years of age (P=

.006) and even in men without history of hypertension or diabetes (P<. 05).[8] Consistent with Ridker, Kuller, and Koenig's results, the HHP underlined that hs-CRP can help predict risk for future MI and stroke occurrence even in healthy populations with no apparent risk factors.

Women and CRP Values

In 1998 Ridker conducted the first trial to determine whether CRP was an independent predictor of cardiovascular disease among healthy women.[9] He followed 39,867 Women's Health Study (WHS) participants consisting of postmenopausal heath professionals with no prior history of MI, stroke, or transient ischemic attack.[9] Of the large sample size, 122 women subsequently suffered a first cardiovascular event in the 3-year follow-up.[9] These women were paired with 244 controls matched for age and smoking behavior.[9] Data revealed that case subjects had higher baseline CRP levels (6.45 mg/L) than control subjects (3.75 mg/L).[9] Women with the highest levels (above 7.3 mg/L) had a 5-fold increase in any vascular event and a 7-fold increase of MI or stroke.[9] Ridker states these results are "most striking" because baseline hs-CRP levels revealed 2.8 to 6.6 increased relative risks in women with no prior history of diabetes, hypertension, or premature atherosclerosis.[9]

Women and Metabolic Syndrome

The metabolic syndrome predisposes patients to diabetes and heart disease. It is characterized by having three or more risk factors including low HDL-C, central obesity, high triglyceride levels, increased blood sugar, or hypertension.[10] Women are the targeted demographic in Ridker's 2002 "C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events." Ridker observed 14,719 healthy subjects with an 8-year follow-up for MI, stroke, coronary revascularization, or CVD-related death.[10] He investigated whether hs-CRP added prognostic value to the metabolic syndrome in predicting cardiovascular events. At baseline, median hs-CRP levels for subjects with 0, 1, 2, 3, 4, or 5 metabolic syndrome characteristics were 0.68, 1.09, 1.93, 3.01, 3.88, and 5.75 mg/L respectively.[10] CRP levels followed a strong linear increase as

the number of components increased. Baseline levels above 3 mg/L at added prognostic information to all levels of metabolic syndrome severity, and relative risk became more apparent with 3, 4, or 5 metabolic syndrome characteristics.[10] Ridker's data reveals that CRP adds important prognostic information to the metabolite syndrome.

CRP and Multimarker Approach

Troponin (TnI) and B-type natriuretic peptide (BNP) have emerged along with CRP as new cardiac biomarkers associated with higher death rates and recurrent ischemic events.[11] While CRP is only an inflammation marker, TnI displays transient elevation during myocardial necrosis and BNP levels rise with left ventricular overload.[11] Published in the 2002 issue of *Circulation*, Marc S. Sabatine's "Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes" investigated the simultaneous assessment of all three biomarkers. Sabatine hypothesized the biomarkers would provide complementary information and enable clinicians to better stratify risks for complications and mortality associated with acute coronary syndrome development.[11] Data revealed combined elevation of TnI, BNP, and CRP identified broader relative risk categories for short (30-day) and long (6-month) term recurrent major cardiac events.[11] Subjects with one, two, or three elevated biomarkers had a respective 2.1, 3.1, and 3.7-fold increase in the risk of death, MI, or congestive heart failure.[11]

CRP and Blood Pressure

Gavin J. Blake and colleagues investigated the link between blood pressure and vascular inflammation in the 2003 "Blood pressure, C-reactive protein, and risk of future cardiovascular events." The study assessed first cardiovascular events in 15,214 women followed for an 8.1-year median.[12] Blake sought to determine whether blood pressure values were independent determinants of CRP levels. He adjusted risk in participants based on age, smoking behavior, and LDL-C levels. Of the 321 women who developed first cardiovascular events, baseline hs-CRP increased linearly with systolic and diastolic blood pressure elevation.[12] The adjusted cardiac hazard

ratio was 8.31 higher in women with blood pressure above 160 mm Hg and hs-CRP above 3.0 mg/L compared to women with blood pressures below 120 mm Hg and hs-CRP below 3.0 mg/L.[12] Women with both high CRP and high blood pressure had a 3.27 higher risk of developing a cardiovascular event than any other group.[12]

Blake's study indicated that both elevated CRP levels and increasing blood pressure categories are independent determinants of future cardiovascular events. The combination of these measures, however, improved risk prediction as CRP raised blood pressure–determined hazard ratios an additional 0.73-0.87 points.[12] In both age-adjusted and risk factor adjusted models, increasing categories of blood pressure correlated with step-wise increases in CRP levels (P for trend < 0.0001).[12] High blood pressure is a major risk factor for atherogenesis and may stimulate endothelial inflammation contributing to plaque formation, but the results of Blake's study only indicate blood pressure and CRP work "in tandem" to increase a pro-inflammatory response.[12] Hirschfield and Pepys suggest that future clinical *in vivo* trials may be able to block CRP binding sites on vessel walls. They hope data can reveal whether CRP is just a marker of inflammation or if it actively participates in atherosclerosis pathogenesis.[2]

CRP and Cholesterol

Cholesterol screening is the primary tool used to evaluate risk of coronary heart disease (CHD). According to Backes's review, however, 35% of CHD patients have desirable cholesterol levels below 200 milligrams per deciliter (mg/dL) and nearly 50% have below average levels (210-220 mg/dL).[2] These statistics suggest cholesterol screening alone may not always identify cardiovascular risk. In the 2002 second Women's Health Study, Ridker investigated whether hs-CRP can add prognostic value to LDL-C levels in predicting cardiovascular events. The study followed 27,939 women for eight years.[13] Baseline hs-CRP and LDL-C levels were evaluated for MI, stroke, and cardiovascular death correlation. Over 77% of cardiovascular events occurred in women with low LDL-C (below 160 mg/dL) and 46% occurred in women whose levels fell below 130 mg/dL.[13] LDL-C and hs-CRP levels were minimally correlated, suggesting that each identified different high-risk groups.[13]

Women with low LDL-C who suffered a cardiac event did not meet primary prevention treatment criteria designed for only high LDL-C patients.[13] Ridker affirms that LDL-C levels are inadequate in predicting cardiac events in individuals with low LDL but high hs-CRP levels. His study confirms that although LDL remains a critical risk factor, hs-CRP is a stronger overall predictor of heart disease and stroke. M.B. Clearfield also emphasizes that cholesterol-screening adjustment is needed to account for individuals with LDL levels below 130 mg/dL but hs-CRP above 3 mg/L.[8] He warns that these individuals are often overlooked, but constitute a high-risk group of over 30 million Americans.[8] In 2001, the National Cholesterol Education (NCEP) Adult Treatment Panel (ATP III) endorsed adding hs-CRP to traditional LDL-C screening in order to improve risk assessment in patients not identified by cholesterol levels alone.[8]

hs-CRP and Clinical Usefulness

According to CDC and AHA guidelines, hs-CRP levels are split into tertiles to represent low, moderate, and high vascular risk. Levels below 1 mg/L reflect low vascular risk, but levels above 10 mg/L may represent nonspecific inflammation and therefore lack positive predictive value.[4] In 2004, Paul M. Ridker and Nancy Cook further investigated the clinical usefulness of hs-CRP levels below 0.5 and above 10 mg/L. Ridker and Cook followed 27,939 women for occurrence of first cardiovascular events over a 9-year follow-up.[4] Their data suggests hs-CRP predictive value extends beyond the 1-3 mg/L range established by the CDC/AHA. Individuals with 10-30 mg/L hs-CRP levels had a 6.3 to 7.6 higher relative risk than individuals within moderate ranges (1-2 mg/L).[4] Ridker and Cook claim such individuals make up 2 to 5% of the total U.S. population and health professionals often misinterpret their hs-CRP's as false positives.[4] Over 15% of the population also displayed values less than 0.5 mg/L, suggesting very low risks of future cardiovascular events.[4] The study demonstrated that hs-CRP levels provide important prognostic information across a full range of baseline values without a threshold effect.

Ridker and Cook's study further revealed hs-CRP is a strong cardiac risk predictor over a full range of Framingham Risk Scores

(FRS). In 1991, the Framingham coronary prediction algorithm was established to predict CHD risk based on an individual developing angina pectoris, myocardial infarction, or coronary disease death over 10 years.[4] Separate score sheets were used for men and women, and age, LDL-C, blood pressure, smoking, and diabetes mellitus were used to estimate relative risk.[4] Ridker and Cook's data indicated the impact of both very high (10 mg/L) and very low (below 0.5 mg/L) baseline hs-CRP levels on future vascular risk remained unchanged even when individual FRS components were adjusted for.[4] FRS-adjusted relative risks further revealed individuals with baseline hs-CRP over 7.73 mg/L had a 2.8 higher RR than individuals below 1.0 mg/L.[4] Ridker observed that subjects with exceptionally low hs-CRP levels had very low risks of future cardiovascular events, raising the possibility that a virtual CRP absence may be protective against CVD development.[4]

Lowering hs-CRP/ Areas of Future Study

Ridker's CRP review, published in the 2003 issue of *Circulation,* warns that CRP is a novel biomarker whose role in cardiovascular health is still under investigation. Ridker cautions that there is no current evidence suggesting a decrease in CRP corresponds with lowered cardiac risk, but notes that it took 20 years before definitive clinical trials demonstrated cholesterol reduction decreased chances of CVD development.[1] He states the "good news" is the best ways to lower CRP include diet, exercise, and blood pressure control, methods already known to decrease cardiac risk.[1] Ridker suggests pharmacological aspirin interventions may also reduce CRP-induced inflammation and decrease the chance of a first heart attack or stroke.[1] Clearfield agrees with Ridker and claims pharmacological intervention can benefit patients with low LDL-C and high hs-CRP.[8] He suggests the use of statin therapy to lower LDL-C levels and thereby reduce the risk of primary cardiovascular events as well as recurrent episodes.[8]

Discussed in Clearfield's review, Ishwarlal Jialal and Michael Albert conducted independent trials assessing statin therapy effects on CRP. Both trials demonstrated that six weeks after statin treatment was initiated, hs-CRP levels decreased 15-28%. [8] Clearfield notes patients with hs-CRP above 12 mg/L derived a two-month

survival benefit from statin therapy, and those with hs-CRP over 17 mg/L conferred benefits within a week.[8] Patients treated with statins within 24 hours of acute coronary syndrome presentation also displayed lower incidence of death, stroke, and reinfarction than those who did not receive treatment.[8] Although statin therapy lowered LDL levels, hs-CRP decline was independent of LDL reduction magnitude.[8] It is still unclear whether individuals with low LDL but high hs-CRP can benefit from statin therapy or whether cardiovascular risk reduction should be assessed solely on hs-CRP. Ridker explains current NCEP ATP III guidelines limit statins only to individuals with known heart disease, elevated LDL levels, above a 20% risk of CHD over 10 years, or known history of diabetes.[1, 8]

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is the first large scale, randomized trial designed to investigate statin therapy use on healthy individuals with high hs-CRP. Ridker initiated JUPITER and subjects began enrolling in February 2003.[8] The study will evaluate if long-term, daily 20 mg rosuvastatin therapy will reduce first major cardiovascular events in individuals with low LDL (below 130 mg/dL) but hs-CRP levels above or equal to 2 mg/L.[8] Subjects will be randomized into drug or placebo groups and a 3-4 year follow up will assess for subsequent cardiovascular death, stroke, MI, angina pectoris, or arterial revascularization.[8] The trial is expected to provide crucial information whether aggressive statin therapy can reduce CVD risk through lowering hs-CRP levels. A positive outcome in JUPITER would validate statin therapy use for 25 to 30 million Americans who fall outside NCEP ATP III treatment guidelines.[8]

Conclusion

Although hypertension, high cholesterol, and diabetes increase the chances of developing CVD, it is still possible to suffer from heart disease without having these traditional risk factors. Starting in the mid 1990s, attention turned to inflammatory biomarkers to help improve early detection of coronary and cardiovascular risks among individuals not identified by lipid screening alone. C-reactive protein has become the most prominent CVD biomarker and a strong independent predictor of myocardial infarction, stroke,

sudden cardiac death, and coronary heart disease. CRP evaluation in individuals 30 years and older can further aid in appropriate pharmacological and lifestyle intervention to prevent first ever heart attack or stroke.[1] A decade of Paul M. Ridker's research has validated CRP's value in identifying high-risk individuals across the full range of Framingham Risk Scores, metabolic syndrome components, and hyperlipidemia factors. Ongoing research like the JUPITER trial can transform CHD treatment practices and can confirm hs-CRP as a potential adjunct for global risk assessment in the primary prevention of cardiovascular disease.

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