Increasing Evidence That Influenza Is a Trigger for Cardiovascular Disease

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(See the Major Article Warren-Gash et al, on pages 1636–8.)

Cardiovascular disease (CVD) is the cause of most premature deaths in more-developed countries. Although conventional risk factors account for much of the population attributable risk of CVD, they are less effective at predicting future cardiovascular events (ie, heart attack and stroke) in individuals since many people without CVD also have 1 or more risk factors present [1]. A possible explanation is the link between infection and atherosclerosis, first suggested a century ago by William Osler [2] and undergoing a resurgence of interest in recent times.

CVD is increasingly considered to be an inflammatory condition, and evidence is increasing that CVD may be triggered by infections. Initial interest in chronic bacterial infections, such as Chlamydia pneumoniae, Helicobacter pylori, or dental infections [3–5], as potential precipitants of acute myocardial infarction (AMI) and stroke has diminished following negative findings from epidemiological studies [6] and therapeutic trials of antimicrobial agents [7–9]. The study by Warren-Gash and colleagues [10] published in this issue gives support to the hypothesis that acute respiratory infection, and particularly influenza, may be a trigger.

The authors used a self-controlled case series method [11] with a novel database (CALIBER) that links hospital data on acute myocardial infection (AMI) and general practice data, including patients presenting with acute respiratory infections. They investigated the risk and timing of first AMI with the timing of preceding acute respiratory infections (ARIs) in patients aged ≥40 years in this primary care population. Importantly, the analysis took into account the likelihood of an ARI being influenza by using predefined medical codes for influenza, the timing of circulating influenza virus, and influenza vaccination status. The authors found that AMI risks were significantly raised in days 1–3 after ARI: incidence rate ratio, 4.19 [95% confidence interval, 3.18–5.53], with the effect tapering over time.

The evidence for influenza as a trigger has increased over the past 3 decades, from recognition of the association between winter infections and CVD, to the temporal association between respiratory infection preceding CVD, pathological evidence of the influenza virus postmortem in heart muscle, and accumulating evidence that preventing infection, particularly influenza, can prevent heart attacks. The evidence, its implications, and gaps in knowledge are briefly summarized below.

An early clue to the relationship between CVD and influenza was found in closely corresponding winter peaks [12] in respiratory infections and CVD. Reichert and colleagues [13] looked at the relationship between peaks in winter mortality from cardiovascular, cerebrovascular, or diabetes-related illness with peaks in influenza and pneumonia deaths over 40 years in a carefully designed interrupted time series study. They found a remarkably consistent pattern. Deaths from these conditions were higher in years dominated by epidemic influenza A virus (subtypes H2N2 or H3N2), rather than by nonepidemic strains. This supported the notion that the deaths were due to influenza, rather than to cold weather, a competing hypothesis [13]. Similar patterns occur in the subtropics, also suggesting that this is not just due to cold stress [14, 15].

It is also known that influenza-related illnesses contribute substantially to the increase in hospital admissions and deaths during winter [16]. Although two-thirds of additional deaths during the influenza season result from respiratory disease (with an increase of up to 55%), around one-third are due to CVD (with an increase of up to 4%). Deaths are 5 times higher in those with CVD and 20 times higher in those with CVD and pulmonary disease, with mortality rates as high as 9% reported among the latter [17].

Moreover, influenza epidemics are associated with a rise in coronary deaths.
confirmed by autopsy [18], and similar seasonal variations have been found in mortality from influenza and coronary heart disease (CHD) [19]. Influenza viral antigens have been identified in autopsy lung samples from patients dying from AMI [20], although other respiratory viruses have also been implicated.

The relationship between influenza (and between pneumonia) and CHD might be a result of patients with CHD being more susceptible to respiratory illness, rather than to or as well as respiratory infections leading to AMI [21], but studies showing that respiratory infection precedes AMI are more suggestive of a causative link.

A number of previous case-control studies have shown this association between AMI and upper respiratory tract symptoms that precede the AMI by up to 2 weeks [22]. These studies have been limited by unknown confounders, recall bias (in studies in which patients and controls were questioned), and the nonspecific nature of the respiratory conditions examined. The new study points to influenza, rather than to nonspecific respiratory infections, as being a more likely trigger of AMI.

The advantage of the self-controlled case series design over other observational designs is that case patients act as their own control in periods when they are not exposed, and this, therefore, eliminates the problems of unmeasured confounding, provided these variables are constant over time within individuals [23]. A previous self-controlled case series study by Smeeth et al [24] found that risks of a first AMI (20 486 cases) and first stroke (19 063 cases) were significantly raised after respiratory tract infection. Risks were highest during the first 3 days and then gradually fell during the next 4 weeks, with incidence rate ratios for AMI of 4.95, 3.20, 2.81, and 1.95 at days 1–3, 4–7, 8–14, and 15–28 after infection, respectively.

Of course, influenza is likely to be a trigger for only a proportion of AMIs. An observational study in one Thai hospital over a year found a prevalence of influenza-like illness in 11.0% of patients (41 of 376) and serologically confirmed influenza in 12.5% of patients (47 of 376) who were admitted with acute coronary syndrome [25]. Further support for a link between preceding respiratory infection and vascular disease relates to the evidence that preceding infection may trigger ischemic strokes [26, 27].

Influenza and other respiratory infections may cause atherosclerosis through nonspecific immune stimulation [28] or plaque rupture [29]. Fever can lead to endothelial dysfunction, hypercoagulability, or increased viscosity. Tachycardia, stress, or changes in metabolic risk factors in response to infection might also be implicated in AMI. Infection may also trigger coronary arteritis, spasm, or thrombosis [30]. The currently favored mechanism is that infection triggers plaque rupture [29], partly mediated through an increased response to inflammatory stimuli in acute coronary syndrome [31].

A key question is whether preventing influenza, particularly by means of influenza vaccination, can prevent influenza-triggered AMI. A recent systematic review of observational and 2 randomized controlled trials [22], together with more recent observational studies [32, 33], suggest that it can, whereas other studies suggest that the effect may be largely due to confounding. Many now consider that further definitive, large-scale randomized controlled trials are needed to resolve this issue [34].

Until we have a clear answer, it seems reasonable to strongly encourage patients eligible for vaccination and who have preexisting CVD to have their annual influenza vaccine.

Notes

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