Task Force IV: Cardiovascular Effects of Emerging Infectious Diseases and Biological Terrorism Threats

Basic, Clinical, and Population Science Research and Training Needs

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Introduction

The role of infectious agents in cardiovascular disease has been well-recognized since the early 20th century (1), when in a few decades, introduction of antibiotics and public health efforts made it possible to control many infectious diseases. Subsequently, considerable attention was paid to the role of multiple noninfectious risk factors in the atherosclerotic process. More recently, investigators have addressed the possibility that infections may complicate existing cardiovascular diseases and advance the atherosclerotic process. It is also possible that exposure to infectious agents and toxins may have more direct cardiovascular effects and play an important role in inflammation (2). The significant role of inflammation in many cardiovascular diseases (2) and the identification of new emerging infections (e.g., HIV, Ebola, SARS, and avian influenza) have renewed interest in the potential role of infections in cardiovascular diseases. Current knowledge of these relationships is largely based on anecdotal reports; no prospective studies or well-developed research programs on this issue are currently available.

Task Force IV discussed issues surrounding basic, clinical, and population science research and training needs with regards to emerging infectious diseases and biological threats. Although some data are available on the manifestations of and therapies for some infectious agents (e.g., influenza) (3) and some preventive interventions have been developed (e.g., smallpox vaccination) (4), little information is available on the cardiovascular effects of most emerging infectious diseases and potential bioterrorism agents. Comprehensive, targeted research is needed to assess the nature and extent of the effects of emerging and re-emerging infections, as well as other biologic threats, such as Category A, B, and C agents,[1] on the cardiovascular system. This research should address clinical manifestations, diagnostic methods, and the efficacy of various preventive and therapeutic interventions. Translational and interdisciplinary research approaches are also needed to analyze data from basic, animal, clinical, and population-based studies to reach a comprehensive understanding of this topic.

The group recognized that lessons can be learned from the effects of both natural and unnatural disasters for assessing the secondary effects of emerging diseases and biological agents on the cardiovascular system (5–7). In general, epidemiologic, clinical, and basic research can help clarify the pathogenesis, identify people at highest risk for potential cardiovascular complications, identify the most effective diagnostic and therapeutic approaches, and establish effective prevention and rehabilitation methods.

In this report, we provide an overview of the limited epidemiologic research that has been conducted connecting cardiovascular and infectious diseases and identify gaps in the literature. We describe the need for surveillance systems that might increase our ability to quickly identify disease outbreaks and track their course and cardiovascular impact. We also address the clinical studies required to improve our ability to diagnose, prevent, and treat the potential cardiovascular complications of bioterrorist agents and diseases, as well as the basic research that could be useful for clarifying the mechanisms of infectious disease. We describe the training needs required for both health care professionals and high-risk members of the public to help them recognize and respond appropriately to bioterrorist threats that could have cardiovascular effects. The report ends with our suggestions for basic, clinical, and epidemiological research and for training for professional and lay populations.

Epidemiologic Studies

Traditionally, epidemiologic or population studies have played a key role in gaining insight into the different aspects of infectious diseases, including emerging or re-emerging infections and their complications. The epidemiologic literature focuses primarily on the immediate morbidity and

[1]Based on the categorization scheme of the Centers for Disease Control and Prevention (CDC). Agents in Category A are the highest priority because they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness. Agents in Categories B and C have lower priority. For more information on this categorization scheme and a list of agents in each category, see the CDC's list of bioterrorism agents and diseases at: http://www.bt.cdc.gov/agent/agentlist-category.asp.

mortality or the long-term noncardiovascular complications of these infectious diseases.

New epidemiologic studies are needed to identify, characterize, and prioritize different classes of emerging infections as well as biological toxins with a potential for causing cardiovascular complications and quantify their cardiovascular burden. These effects may be direct or indirect, or even occur as iatrogenic complications of preventive or therapeutic efforts. These infections may occur sporadically or in epidemics or pandemics (8–12). They may occur naturally (e.g., epidemic and pandemic influenza, West Nile virus), accidentally (e.g., accidental release of smallpox virus), or through acts of bioterrorism (e.g., smallpox, anthrax in the U.S. in 2001, and ricin) (9,13–16). Also worthy of consideration are potential side effects of mass public health interventions, such as smallpox or anthrax vaccination, in response to potential threats (4,17,18).

Infectious disease outbreaks have been associated with excess cardiovascular mortality (19–21). Epidemiological studies are needed to identify both the acute (e.g., assessment of influenza epidemics) and potential chronic effects (e.g., increased risk of atherosclerotic events) of such outbreaks (22). Studies of available data on cardiac patients after major disasters such as earthquakes or the September 11, 2001, attacks could be helpful in predicting the long-term psychological and other effects of other events such as infectious disease outbreaks or biological threats on individuals with existing cardiovascular disease (23–25).

Available databases and retrospective studies should be used to assess whether historical outbreaks of infectious diseases and interventions to control them (e.g., flu epidemics, SARS, smallpox vaccination programs) were consistently associated with an increase in cardiovascular complications (19–21,24,26–29). When possible, such studies might examine issues such as identifying the excess risk of cardiovascular complications associated with each threat, time–response relationships, whether the disease is associated with both long-term chronic cardiovascular effects and acute effects, and whether certain populations have an increased risk following such events. Potential data sources include death certificates, clinical examinations of survivors, medical records, emergency room admission records, and billing records. Predefined criteria should be established to identify whether the number of cardiovascular events actually increases following an outbreak, assess possible cause–effect relationships, and evaluate the impact in vulnerable populations, such as persons with pre-existing cardiovascular disease or atherosclerosis.

Emerging infections may have primary or secondary effects on the cardiovascular system. The primary impact of a disaster should be evaluated in the immediate vicinity of the threat. Indirect and secondary impacts (such as psychological effects) may be evaluated in locations that were not direct targets of the event. These psychological evaluations should be incorporated into an evaluation program designed to assess cardiovascular implications, because they could have a significant impact on the pathogenesis of cardiovascular disease and have implications for therapy (30–32).

Research Infrastructure for Surveillance and Response

When indicated, a cardiovascular component needs to be designed and implemented into surveillance systems at regional, national, and global levels to increase our ability for early detection of cardiovascular effects of diseases of interest (33). Surveillance should also include monitoring of disease outbreaks in animals for diseases affecting nonhuman hosts (34).

Syndromic surveillance is comprised of systems designed to detect in a timely manner signals of increasing events based on monitoring patterns of hospitalizations, emergency room visits, emergency medical services data, billing records, prescriptions, and so on (35–38). Adhering to standard national protocols for data definition and collection, as well as ensuring compatibility of electronic medical record systems, are critical factors for developing syndromic surveillance systems. State and federal law should permit syndromic surveillance to ensure morbidity and mortality follow-up because syndromic surveillance may often include cardiovascular data and can potentially detect disease outbreaks sooner and with a higher sensitivity than traditional surveillance systems, which depend on active reporting of diagnosed cases (38–41). The growing use of electronic medical records could facilitate timely surveillance and easy inclusion of cardiovascular data.

In the meeting the group discussed that although issues of privacy and confidentiality are important, the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 allows necessary disclosures of protected personal health information to public health authorities for the purpose of preventing or controlling disease, injury, or disability.

Clinical Studies

Very little information is available about the likely impact of most emerging infections and potential bioterrorism agents on the cardiovascular system. Most prior studies have concentrated on noncardiac effects and few experimental studies have been done. Clinical studies, therefore, are needed to assess the pathophysiology of each threat's impact on the cardiovascular system and its components (28).

Potential cardiovascular effects of emerging infectious diseases and biological threats include damage to the myocardium, endocardium, pericardium, and blood vessels; destabilization of vulnerable plaques; accelerated progression of atherosclerosis; modification of risk factors; valvular damage; conduction system abnormalities; prothrombotic effects; and psychological sequelae. Bioterrorism agents may serve as a primary cause of cardiac disease in people without pre-existing cardiovascular disease and may have secondary

cardiovascular effects in populations with atherosclerosis or other chronic cardiovascular diseases.

It may be possible to conduct clinical trials/observational studies in healthy volunteers for low-risk interventions (e.g., smallpox vaccination in military service members) (17,28). Clinical observations and case series in the setting of disasters may be feasible, but these will be unplanned and unpredicted (26,27). When experimental studies are impractical or not possible for ethical reasons, disease effects may be monitored in subjects with known exposures or who are at high risk for exposure and in health care professionals caring for exposed people. Cardiovascular effects should be carefully recorded and subjects' responses to different interventions should be monitored. Careful monitoring of these groups may help develop diagnostic methods for rapid identification of an emerging infectious disease or terrorist threat and facilitate the identification of effective preventive or therapeutic interventions.

Examples of potential natural experiments include studies of military personnel after experimental vaccinations and treatments and of individuals who have survived disasters, as well as long-term follow-up of people who have survived infections (e.g., influenza, anthrax) (28). To study the cardiovascular effects of mass smallpox vaccination efforts, for example, investigators could monitor electrocardiography, echocardiography, and troponin measurements in a subset of asymptomatic subjects following smallpox vaccination. Different risk groups could be followed to determine whether the number of cardiac events increases after the vaccine is administered. Different therapeutic measures could also be assessed in these individuals, and the results could be compared to yield the best strategy. Since plaque disruption has been proposed as an etiology for cardiac effects, analyzing the mechanisms of known plaque disruption triggers could yield a pathogenesis model of infectious etiologies (24,25,32,42).

In addition to specific therapies for each infectious agent (e.g., antibiotics against specific infectious agents, antidotes for toxins), nonspecific cardioprotective medications may be tested in these natural settings. Recent reports suggest potential benefit from the use of beta blockers for immediate survivors following major stressful events to reduce the risk of posttraumatic stress disorder (43). Beta blockers may also be effective and merit further research in preventing acute coronary syndromes, especially in high-risk patients, following terrorist events or disasters. Other potentially effective therapies for various cardiac complications include aspirin, antiplatelet drugs, anti-inflammatory drugs, and intravenous immunoglobulins. The efficacy and cost–benefit ratio of such interventions when many patients are already receiving these drugs are largely unknown.

Outbreaks of emerging infections are unpredictable, and it is difficult or even impossible to make substantial changes in the clinical care of high-risk individuals within a short time period. Therefore, considerable effort should be focused on increasing the adoption rate of proven preventive therapies in people with cardiovascular disease to decrease their likelihood of cardiovascular complications in a crisis. For example, the best way to improve vaccine coverage rates during influenza pandemics is to improve interpandemic vaccine coverage rates (44).

Vaccination

Although the influenza vaccine has been shown to reduce the risk of cardiovascular events (3), a small number of cardiovascular events have been reported following smallpox vaccination, including myopericarditis and rare ischemic events associated with pre-existing atherosclerotic disease or risk factors, although the relationship of acute myocardial infarction to smallpox vaccination is uncertain. The cardiovascular effects of vaccines for other infectious agents are not readily recognized; however, as new vaccines are developed and used, their cardiovascular effects should be closely monitored. With any vaccination, a general stimulation of the immune system could cause a flare-up of the inflammatory process in the atherosclerotic plaques, endocardium, myocardium, or pericardium, exacerbating inflammatory disease. Also, the widespread activation of inflammatory cells could be associated with activation of macrophages in vulnerable plaques, triggering heart attacks. Therefore, an increased early hazard is a possibility after any vaccination program and needs to be monitored and ruled out if possible. However, B-cell activation (part of the humoral response) may be protective against atherosclerosis (45). Research is needed on the potential cardiovascular benefits and complications of immunization and on public attitudes regarding the benefits and risks of vaccination in general.

Clinical Guidelines

Recommendations on the diagnosis, prevention, and treatment of cardiovascular complications of biological threats are critically needed. When applicable, consensus guidelines for different infectious agents that could be used for bioterrorism (14,46–50) should address cardiovascular effects and the related diagnostic, preventive, and therapeutic approaches.

Basic Studies

In the absence of controlled clinical experiments and given the high-risk nature of many threats that make clinical studies either difficult or impossible, basic laboratory and animal studies may provide valuable information on the cardiovascular mechanisms of infectious disease and help prepare for bioterrorism threats.

The availability of several good animal models of atherosclerosis should enable scientists to determine the effect of many infections and biological toxins (e.g., ricin) on atherosclerotic plaques, the coagulation system, circulatory and hemodynamic components, and the conducting system (51–54). Infections may trigger acute destabilization of

vulnerable plaques, leading to acute coronary syndromes (in short-term) or they can accelerate the atherosclerosis process and increase patients' risk over years (3,51,55,56). The efficacy of different classes of medications in preventing complications could also be assessed in these animal models.

Training

Professional Training

Training strategies should target professional leadership, workforces, and organizations. Issues of the cardiovascular effects of emerging infections need to be added to and incorporated into existing training programs. These educational programs may also be incorporated into continuing medical education programs for health care providers.

When applicable, a cardiovascular component may be incorporated into current infectious disease and biologic agent outbreak training programs. Consensus-based recommendations for responding to different bioterrorist threats describing the measures to be taken by medical and public health professionals can be used as educational materials for this purpose (14,47–50,57).

Public Education

As the first and third leading causes of death in the U.S., Task Force IV members noted that cardiac and cerebrovascular events will continue during infectious disease outbreaks and bioterrorist events. Individuals who have or are at risk for cardiovascular disease should adhere to the well-documented evidence-based guidelines for primary and secondary prevention of cardiovascular diseases (such as those developed by the American College of Cardiology and American Heart Association) (58–60). The best way to ensure that patients will follow these guidelines at the time of a crisis is to improve general adherence to these guidelines. The public can provide additional protection for those at risk of cardiovascular complications by learning cardiopulmonary resuscitation techniques and how to use automated external defibrillators (61). Educational materials should be developed for the public regarding the potential impact of emerging infectious diseases and biological threats on cardiovascular disease.

Future Considerations

Based on this discussion of the research and training needs related to the cardiovascular effects of potential bioterrorist agents, Task Force IV suggested that addressing the following issues may help to improve response and cardiovascular outcomes of potential emerging infectious diseases and biological threats:

1. Multidisciplinary translational research should assess the full spectrum of the effects of potential bioterrorism agents on the cardiovascular system.
2. To determine the incidence and significance of cardiovascular complications of smallpox or other vaccinations, epidemiologic studies should be conducted in conjunction with vaccination programs, and animal studies should be conducted to further delineate the extent and nature of potential cardiovascular complications.
3. Public health surveillance should be established to monitor incidence and trends of cardiovascular diseases. The proposed surveillance system should be capable of detecting increased rates of cardiac events (e.g., acute coronary syndromes, myocarditis) with high sensitivity and in a timely manner. Following relevant events (e.g., massive vaccination programs or disease outbreaks) with a high risk for cardiovascular adverse effects, reporting of cardiac complications should be encouraged and even required. The feasibility of reporting cardiac events following relevant events should be explored. Privacy and legal issues need to be addressed.
4. When applicable, a cardiovascular disease response component must be incorporated into response plans for emerging infections and bioterrorism events with potential adverse cardiac effects. Health care providers and first responders should be trained about the common and important cardiac effects of emerging infections. Related scenarios should be tested in drills and tabletop exercises. When necessary, educational material on potential cardiac effects of biological agents should be developed for the public and made widely available.
5. An influenza pandemic is considered likely to occur and, therefore, must be considered a high-priority research issue. The lessons learned in trying to prepare for such a pandemic might be applied to preparations for outbreaks of other emerging infections and bioterrorist threats.
6. The legal and ethical issues regarding equitable distribution of scarce resources to cardiac patients at times of crisis require attention, and solutions for different scenarios should be outlined.
7. Environmental safety procedures for catheterization laboratories and coronary or intensive care units that care for patients infected with highly contagious agents must be defined and implemented.
8. In the absence of clinical trials, the role of vaccination, antitoxins and anti-infective therapy, and nonspecific cardioprotective therapies in bioterrorism threats should be analyzed and published by consensus panels.
9. Research is needed on public attitudes regarding the benefits, risks, and acceptance of vaccination from a cardiovascular point of view.
10. Animal models should be used to evaluate the cardiovascular effects of potential threats related to emerging infections (e.g., avian influenza or smallpox vaccine) as well as the efficacy of preventive and therapeutic measures.

Conclusions

Natural outbreak of emerging infections or release of biologic agents during a bioterrorism attack could have a considerable impact on the cardiovascular systems of those exposed to the agents, but little information is available on related mechanisms, clinical presentations, or appropriate diagnostic, preventive, and therapeutic measures. Therefore, research on these issues is needed at the population, clinical, and basic science levels. In addition, health care providers need training on how to identify and care for those who experience cardiovascular effects from a bioterrorist attack.

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APPENDIX 1. ACCF/AHA/CDC CONSENSUS CONFERENCE REPORT ON EMERGING INFECTIOUS DISEASES AND BIOLOGICAL TERRORISM THREATS: TASK FORCE IV—RELATIONSHIPS WITH INDUSTRY

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