LETTER FROM THE EDITOR

Dear Readers:

This month, *Re-flections* features two articles that I hope will stimulate your interest. The first, written by Dr. Oscar Cartaya, provides an in-depth analysis of the risk related to a possible Avian Flu epidemic. This article discusses the specifics of the H5N1 virus' characteristics and sheds insight into pandemic projections.

The second article, written by Dr. Sharylee Barnes, provides very practical information on a cardiac test that is expected to be used more often in the near future. This is the Coronary Computed Tomography Angiogram (CTA) test. Dr. Barnes discusses the value of this test and compares it to other more traditional cardiac tests.

Please enjoy this issue of *Re-flections.*

J. Carl Holowaty, M.D.
cholowaty@rgare.com

AVIAN INFLUENZA: REVIEW OF BASIC VIRUS DATA, AND PANDEMIC CONTROL PLANNING

By Oscar A. Cartaya, M.D.

The avian influenza virus has been the subject of intense media scrutiny, with projections for a major pandemic causing a very high level of mortality being commonly presented. How much of this media coverage and projections are likely to actually occur is a subject of major concern. The present article reviews the scientific information available on the virus and the medical care available to deal with such an outbreak. There have been remarkable medical advances during the last century that will impact the outcome of any such pandemics. I believe that although no firm conclusions can be reached at this time on the possible mortality outcome of an avian influenza pandemic, review of the available scientific information supports a more optimistic view of the possible mortality outcome than current projections allow.

As of November 29, 2006, there have been 258 confirmed human cases with this type of influenza, with no documented instance of human-to-human transmission of this virus (Table 1). The possibility of a mutation that allows transmission of this virus between humans is widely feared: Many are concerned that this virus may eventually cause a major pandemic, mirroring the high mortality rate of the 1918 flu pandemic. Avian viruses cannot normally infect humans; they cannot attach to human target cells. A major mutation of the avian influenza virus would be required before the virus would become capable of infecting humans, as occurred in the 1918 pandemic. The new avian influenza virus has been compared with the 1918 influenza pandemic virus, and there is widespread speculation that the new virus may eventually have similar effects.

This review references two specific influenza viruses: the current avian influenza virus and the 1918 pandemic virus. Both viruses are of avian origin and both are capable of infecting humans with lethal results. There are many more strains of avian influenza viruses that cannot cross over and infect humans; however, they have no relevance to this review, as they are infective only to birds and not to humans.

There is no doubt the current avian influenza virus can be lethal to humans. Table 1 summarizes the worldwide outcome of human infection with this virus. This table, provided by the World Health Organization[11], offers additional information of interest: First, it is clear that the mortality outcome of infection with this virus is not uniform from country to country. This is presumably due to variations in the level of medical care available in those countries to treat patients with this disease. This variability in mortality rates between countries may also indicate that access to adequate medical care is of great importance and that those patients who lack it will have a higher mortality rate. Secondly, it is interesting to note that Vietnam, which had the largest number of cases up to 2005, totally eliminated any further incidence of this disease in 2006 as a result of large-scale poultry culling programs. Indonesia, on the other hand, has refused to cull infected poultry; as a

result, the incidence of human avian influenza in Indonesia has continued to increase in 2006. This evidence supports the view that the avian influenza virus does not have an intrinsic mortality rate, and that the mortality rate outcome can be controlled through adequate medical treatment, and appropriate public health preventative measures (e.g., culling of infected poultry).

These factors have not been considered in recent publications on the avian influenza virus. Many projections of the potential death rates resulting from a pandemic with this virus are based on computer models using rates of infection and mortality derived from the 1918 pandemic. These computer models make this new potential pandemic appear as a disaster comparable to the 1918 pandemic. These projections are questionable.

Virus Data

Similarities and Differences

First, we should examine what is known about the 1918 pandemic virus and the current avian influenza virus. Both are influenza viruses. As is the norm with influenza viruses, infectivity and capacity for spread depends upon the hemagglutinin protein in their capsules.

Both the 1918 pandemic virus and the current avian influenza virus are influenza viruses of avian origin. The knowledge of the current influenza viruses has been gained from analysis of current viral isolates. Studies of the 1918 pandemic virus were not possible until recent work done by Tautenberger and associates[7] which, in effect, reconstituted the complete genome of the 1918 virus and reassembled it from genetic material fragments isolated from tissue culture and old specimens. Using the reconstituted virus, it was determined that a sequence change of 10 amino acids in the hemagglutinin surface protein was responsible for making this virus easily transmissible to humans, and between humans. The mutation in this case was a sudden genetic shift that occurred spontaneously in this virus. Comparing the 1918 virus to the current avian influenza virus, it was determined that a similar but not identical sudden genetic shift had occurred in the current virus. In fact, some of the same amino acids were changed in the current virus as had changed in the 1918 virus. This discovery supports the contention that the current avian influenza virus can cause a major pandemic, possibly similar to the 1918 pandemic.

However, important differences also were discovered between the two viruses. The hemagglutinin surface protein of the influenza viruses has been studied extensively over the years. This is the protein that is responsible for the ability of the influenza virus to attach to and enter (infect) target cells; it is also responsible for the location of the target cells

to which the virus can attach itself. The hemagglutinin surface protein has been divided into 16 subtypes, only three of which -- H1, H2, and H3 -- have been implicated in major pandemic influenza outbreaks. The 1918 virus was an H1 virus; the current avian influenza virus is an H5 virus.

Influenza viruses are transmitted between humans by two main routes. The primary transmission mode is via airborne transmission, with the virus carried by minute droplets of fluid produced when an infected person coughs or sneezes. The secondary route is through hand-to-mouth contact, with the hands being infected by coming in contact with secretions from an infected person. Both of these methods of transmission will easily bring viruses in contact with upper respiratory tract cells, but not with lower respiratory tract cells (alveolar cells or terminal bronchiole cells).

The 1918 virus H1 protein was a major factor in the mortality caused by this virus. It targeted readily accessible upper respiratory tract cells, and had a very different (from normal human H1 viruses) and very effective attachment site that allowed it to spread very rapidly, with devastating consequences. This virus also had the capacity to reproduce very rapidly after it had penetrated the target cells. It has been calculated [5,9,10] that the 1918 virus was able to produce nearly 40,000 times more viral particles in lung tissue than normal contemporary human influenza viruses. This extremely fast reproductive capacity produced profuse secretions, edema, and hemorrhages in the tissue infected by the virus and caused pulmonary edema and alveolar hemorrhage. The 1918 virus was able to reproduce itself at such a high rate that it flooded the host organism with viral copies that infected and reinfected already infected cells and caused them to swell and burst. Influenza viruses with normal rates of reproduction do not exhibit such extreme effects in invaded tissue.

The current H5 avian influenza protein[4] targets lower respiratory tract cells located in the terminal bronchioles and the alveoli. This makes infection by this virus difficult to achieve. The respiratory tract is designed to prevent free-floating particulate materials in the air, including viruses, from reaching the alveoli. The constant division of the bronchial tree into smaller-diameter segments going in different directions follows a fractional geometry pattern, resulting in no linear path between the exterior environment and the alveolar sacs. As the air is inspired, it follows a recursive path through the bronchial tree which maximizes the chance for any particular matter in the inspired air to hit the walls of the bronchial tree and be trapped by the mucus and secretions in the walls. Once trapped, the mucus containing the particulate matter (viruses and other external materials) is propelled outward by ciliar action and eliminated. Therefore, it is quite difficult for the current H5 avian influenza virus to reach its target cells and establish a site of infection in a human host. This

is a major factor that prevents easy transmission of this virus between humans.

Once the current H5 influenza virus has reached its target cells and infected a human host, it has a number of genetic characteristics that makes it lethal. Among these, it has resistance to interferons; it codes for thick and tenacious mucus production; and it is able to attach easily to other nearby target cells. Hemorrhage, edema, and widespread cell bursting have not been characteristic features of this virus, and its reproductive rate is within the normal range for human influenza viruses and is not close to the rate of reproduction of the 1918 virus.

The results of an infection with either the H1 or the H5 virus are quite different. The 1918 virus spread very rapidly and caused respiratory failure through a complex mechanism including production of an overwhelming level of infective particles, cellular edema, and hemorrhages. Large numbers of people were infected because of the extraordinary level of viral production, the easily reachable cell types targeted by this virus, and its strong attachment to target cells. An abnormally high proportion of those infected developed respiratory failure and secondary bacterial infections. Both the transmission rate and the mortality rate were very high with the 1918 pandemic virus.

The current H5 avian flu virus cannot be transmitted effectively between humans because of the location of the cells it targets. Once established, this virus causes respiratory failure through a mechanism including fluid pooling in the lower respiratory tract. With this virus, the transmission and rate of infection are low, because of the poor accessibility of the target cells; once infected, however, a large percentage of the patients may die from this disease.

Genetic Change

It is clear that the current H5 avian influenza virus may not spread rapidly among humans because of the inaccessibility of its target cells. However, it is well-known that influenza viruses mutate and change, sometimes quite rapidly. This process of change is well-studied and involves either genetic mutation or genetic reassortment. Genetic mutation is an actual change in the genetic material of the virus. Minor genetic changes (called antigenic drift) are the most common types of mutations, but produce only minor changes in the characteristics of the virus. Major mutations (antigenic shift), like the sudden replacement of the hemagglutinin protein by a new subtype, are rather rare and unpredictable events.

Genetic reassortment is the term for the other main mechanism that can alter the genetic characteristics of influenza viruses. This process requires the simultaneous infection of a single target cell by two different strains of influenza viruses. Since the viral components being manufactured by the infected cell are not strain-exclusive, the host cell will assemble new viruses with parts chosen at random from whatever viral parts are available without regard for the viral strain of origin. This process results in new strains of viruses with genetic characteristics of both of the viruses that originally infected the target cell. It would be a most unlikely event to have viruses that target both upper and lower respiratory tract cells simultaneously infecting a single cell. Genetic reassort-

Table 1. Cumulative Number of Confirmed Human Cases of Avian Influenza A/(HSN1)
Reported to WHO (November 29, 2006)

	2003		2004		2005		2006		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	0	0	0	0	0	0	8	5	8	5
Cambodia	0	0	0	0	4	4	2	2	6	6
China	1	1	0	0	8	5	12	8	21	14
Djibouti	0	0	0	0	0	0	1	0	1	0
Egypt	0	0	0	0	0	0	15	7	15	7
Indonesia	0	0	0	0	19	12	55	45	74	57
Iraq	0	0	0	0	0	0	3	2	3	2
Thailand	0	0	17	12	5	2	3	3	25	17
Turkey	0	0	0	0	0	0	12	4	12	4
Vietnam	3	3	29	20	61	19	0	0	93	42
Total	**4**	**4**	**46**	**32**	**97**	**42**	**111**	**76**	**258**	**154**

Total number of avian influenza cases includes number of deaths.
WHO reports only laboratory-confirmed cases.

From: World Health Organization (WHO)

ment is not likely to produce the kind of changes needed to increase the transmissibility between humans of the current H5 avian influenza virus.

It must be understood that for the current H5 avian influenza virus to become easily transmitted between humans, its target cell location must change to an easily accessible location. Since genetic reassortment is not a likely mechanism to cause this to happen, and antigenic drift is not likely to cause such a major change, it is only through antigenic shift that such a change may occur. As described above, this would be a rare and unpredictable event.

A new strain of the H5 avian influenza virus that does not respond to experimental vaccines made against the current H5 avian influenza virus has been reported in China. This virus is reportedly capable of infecting humans but cannot be transmitted between humans. It is thought that this new strain resulted from a process of antigenic drift. Other such strains with relatively minor genetic changes must be expected in the future. Until a major genetic change occurs in the H5 avian influenza virus, the review presented in this paper is valid.

Conclusions Regarding the H5 Avian Influenza Virus

Based on the discussion above, we can conclude the likelihood of the current H5 avian influenza virus to cause a major pandemic is slim, unless a rather rare and major antigenic shift occurs that changes its target cell location. However, in nature and in medicine, it is not possible to predict the events that will happen with absolute certainty, and the potential for widespread mortality caused by any major outbreak of this disorder is very high. Therefore, it is necessary to prepare for a serious outbreak prior to its occurrence

Pandemic Control

Detection and Response Triggering

Controlling a major infectious epidemic outbreak, particularly one caused by a potentially lethal microorganism, is a vast undertaking that requires multiple levels of intervention and expertise. This is particularly true with organisms that spread rapidly. An influenza outbreak, particularly a pandemic influenza outbreak, would be extremely difficult to control. It must be kept in mind throughout this part of the review that the types of actions and interventions required may be disruptive and cause significant economic loss to certain parties. Therefore, the action plan to deal with an influenza pandemic cannot be executed until there is positive confirmation that such an infection is present and spreading rapidly within the U.S. population.

The first priority to deal with an H5 avian influenza outbreak

is to develop an adequate early-warning system. This system must be capable of identifying and confirming the existence of active human cases and rapid spread of the infection. This requires the development of a testing procedure that is fast (with a confirmation time scale of hours, rather than days or weeks) and very accurate. Such a system is already in place and ready for action in the United States. The FDA has approved a prepackaged detection kit for H5 influenza viruses using PCR technology[1], and a national Laboratory Response Network has been established for confirmation of cases of human infection with the H5 avian influenza virus. The vast majority of the clinical laboratories located in mid- to large-size acute care hospitals possess PCR testing equipment and also can make an accurate identification of this virus in clinical specimens. We are currently ready to rapidly identify human cases with H5 avian influenza in the United States, and to trigger a planned response if rapid spread of this disease is confirmed.

Vaccines

Detection and confirmation of the initial stages of an H5 avian influenza outbreak is just the first part of the process. The next step is crucial: effectively slowing the rapid spread of this disease to allow vaccination of as many uninfected people as possible. Much has been written about the various forms of early treatment that are available to treat H5 avian influenza, but the primary mode of prevention and treatment is still vaccination. Of course, a vaccine against a given strain of influenza cannot be produced overnight; it takes a minimum of six months to develop a vaccine against a new influenza strain using conventional methods. Since we know the present strain of H5 avian influenza is not capable of effective human-to-human spread, it must mutate into a new strain before it can cause a major outbreak. Vaccines produced against the present strain of this virus are likely to be ineffective to prevent infection.

Extensive work has been recently performed with "non-matched" vaccines. The reconstituted 1918 pandemic virus is capable of infecting swine and mice as well as humans. Mice immunized with vaccines against other human H1 influenza strains (A/Texas/36/91 and A/New Caledonia/20/99) develop partial protection against the 1918 pandemic virus and can survive lethal doses of the 1918 virus[10]. This is a major advance in the field and a finding holding great promise toward control of future influenza outbreaks.

Another area of great promise in the field of vaccination against influenza is the development of vaccines based upon recombinant subviral particles. Treanor et. al. reported the initial phases of testing of a vaccine to a subviral H5N1 particle[8]. The test was successful with the humans developing protective antibodies to the H5 and N1 antigens in adequate

amounts. This experimental vaccine must be refined (by optimization of antibody production and the use of adjuvants) before it can be made commercially available. Work such as this provides a great deal of hope that an effective "non-matched" vaccine capable of providing protection (at least against death, if not against the actual infection with the virus) can be made available and be ready for use in adequate amounts prior to a major outbreak of an H5 avian influenza pandemic.

Quarantine

Quarantines are another area in which new research has provided applicable solutions to control a major H5 avian influenza outbreak. The classical concept of quarantine is unlikely to be applicable in the context of a modern and very mobile society. However limited forms of quarantine may be applicable forms of control. Metastudies and large-scale modeling techniques indicate that relatively minor restrictions on travel and congregation, particularly in terms of school closures, may significantly slow the rate of spread of the disease[2]. These restrictions will not prevent the spread of the disease, but they will make the spread more gradual, in effect buying time for large-scale vaccination programs (presumably with "non-matched" vaccines as used in this model) to take place. There is a striking graphical representation of this model available over the Internet[3], showing a lower incidence of the disease and a more gradual course of the epidemic.

Medical Care and Treatment of Respiratory Failure

The net effect of these interventions and early-warning systems is not only to prevent people from becoming infected, but to retard the spread of the disease and maintain the number of active cases within the handling capacity of the available health care facilities. This is a very important outcome. Influenza causes death through a mechanism involving respiratory failure and eventual cardio-respiratory collapse. Respiratory failure is caused by the filling of the lungs and the bronchial tree with mucus and secretions, acting together with obstruction caused by cellular inflammation produced by the infection. Once a patient reaches this state, ventilatory support is required to prevent death. A retrospective study of all hospital discharges in the state of Maryland from 1992 to 1995 (over two million hospitalizations) yielded approximately 2,000 cases of respiratory failure[6]. The majority of those who did not or could not receive ventilatory support died. Even with ventilatory support, more than 30% of the patients with this condition died. If a major H5 avian influenza pandemic occurred, one of the major determinants of overall mortality would be the availability of ventilators available to support patients developing respiratory failure. It must be noted that if the time frame of the pandemic were short in duration, the number of cases requiring ventilatory support simultaneously would increase, perhaps exceeding the available capacity of

ventilatory support. If this occurred, the overall mortality rate of an H5 avian influenza outbreak would markedly increase. By taking measures to spread the incidence of new cases over a longer period of time, the number of patients developing respiratory failure and requiring ventilation would also be spread over a longer period of time, allowing the hospitals and health care facilities to provide ventilatory support to greater numbers of patients. In this case, the overall mortality rate of an H5 influenza outbreak would be reduced.

Mortality Rates

Success in controlling a major H5 avian influenza outbreak can be measured by the excess mortality rate resulting from it. A certain number of deaths cannot be prevented, even under optimal conditions. The yearly influenza epidemics result in a direct mortality of approximately 15,000 deaths. The mortality is much higher than this during major epidemics, or epidemics with a particularly virulent organism. During a pandemic, the death rate rises to an average of 0.1% of all infected cases. However, this can also change with a pandemic caused by a very virulent organism: For example, during the 1918 pandemic, the overall mortality was 2.5% of all infected persons.

Mortality during an influenza outbreak has been highest among the very young and the very old and infirm. Although no statistics are kept relating availability of medical care and mortality rates, we believe availability of medical care, particularly ventilatory support, is a major determinant of mortality risk during an influenza pandemic. People living in areas with limited access to medical care or low availability of ventilatory support are likely to have a higher mortality rate. These are the groups that will have the highest mortality risk during a pandemic.

Occasionally, specific influenza outbreaks can exhibit atypical mortality patterns. During the 1918 pandemic, the mortality rate was high among young adults; the cause for this increase in mortality among young adults is not known, and has not been observed in other outbreaks.

Advances in Medical Care Since 1918

The ability to provide medical support and care to people with influenza has markedly improved since 1918. In 1918, there was no knowledge of coronary artery disease; no ventilatory support capacity; no ability to deal with arrhythmias; no ability to provide adequate hydration and electrolyte balance; no antiviral drugs; no antibiotics; and no effective vaccines against influenza. Therefore, the mortality results of the 1918 pandemic must be considered to represent the mortality results in an untreated outbreak. It must be noted that a significant number of the deaths in 1918 were caused by secondary bacterial infections and pneumonias for which there was no effective treatment at the time.

Currently, we have effective influenza vaccines capable of providing protection against death (even if "non-matched"); effective antibiotics to control secondary bacterial infections; adequate techniques for life support and fluid balance; and an elaborate knowledge of cardiac physiology and arrhythmias together with effective treatments for such. It is not reasonable to project a mortality rate comparable to that experienced in the 1918 pandemic for any new influenza pandemics treated with modern techniques.

Conclusions

We have valid reasons to be cautiously optimistic about the prospects for the outcome of a possible new pandemic caused by the present H5 avian influenza virus. Given the data presented about the current virus in comparison with the 1918 virus, it is not at all certain that the present virus will cause a major pandemic. Even if the present H5 avian influenza virus were to mutate and become readily transmissible among humans, there is no convincing indication that it will be as lethal as the 1918 pandemic virus. Should an outbreak occur, numerous factors will impact the final outcome, including the combined effects of the measures in place to identify an H5 avian influenza outbreak and take early action; preparations for mass vaccinations (possible with "non-matched" vaccines); restrictions of congregation and travel aimed to lower the spread of the disease over a longer amount of time; and the marked advances since 1918 in our capacity to medically care for this condition and provide adequate ventilatory support to infected persons.

Based upon this review of the available data and preparations to deal with this outbreak, it is likely that we will be able to keep the overall mortality in line with the mortality observed during other pandemics in the later years of the 20th century (an overall mortality of 0.1% of the infected group). Furthermore, if such an H5 avian influenza pandemic were to occur, it is likely that peak mortality will occur among the very young and the very old and infirm; in addition, persons living in isolated areas or not having access to adequate medical care may experience a higher mortality rate. The evidence suggests that the disaster scenarios outlined in today's news media predicting a very high mortality rate equal to or higher than the mortality rate recorded in the 1918 pandemic for this new potential H5 avian influenza pandemic are not supported by the available data, and have a very small likelihood of becoming true.

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CARDIAC CT ANGIOGRAPHY

By Sharylee Barnes, M.D., DBIM; Medical Director, RGA

The Cardiac Computed Tomography Angiogram (Cardiac CTA) has appeared in life underwriting medical reports lately. Recent technological advances put Cardiac CTA in a position to become highly favored by clinicians and patients alike. The reason is that Cardiac CTA is non-invasive, detailed, accurate, fast, and less expensive than the gold standard of coronary artery imaging by catheterization.

The procedure is new enough that a single familiar name for the test has not emerged. Consequently, underwriters will see a multitude of terms being used including:

- Computed Tomography Angiogram
- Coronary Computed Tomography Angiogram
- CT Angiography
- Coronary CTA
- Cardiac CT
- Cardiac CAT Scan
- Multi-Slice CT Angiography
- Multi-Slice CT Scanning
- Multi-Detector CT Scanning
- MD-CTA
- or any combination of all or some of the aforementioned terms.

Sometimes in an APS received for underwriting, only a few letters (CTA) alert the underwriter that a cardiac evaluation is planned for the proposed insured. To add to the confusion, the newer CT scanning machines may be used to assess cerebral, carotid, pulmonary, and renal vasculature, so the term angiography needs context.

Computed tomography is not new, but its technology is continually being refined. The basic X-ray consists of a focused image being made at a particular tissue depth in order to create a thin cross-sectional view (slice) of the tissue to be studied. Serial cross-sections are done creating multiple images. In addition, the X-ray tube rotates around the tissue in a spiral pattern so the cross-sections are from a multitude of angles. From all this X-ray data, the computer generates high-resolution, 3-D images that resemble a photograph.

Each rotation performs a number of images. Within the past few years, machines have been developed that obtain 16 slices per rotation, the number needed to get clear images of the coronary arteries. The advent of 64-slice machines achieves remarkable detail. At three rotations per second, a multi-slice CT creates up to 192 slices per second!

Speed is important because the scanner captures an image of a moving object, the beating heart. Speed *freezes* the image, like a fast shutter speed on a camera. The resolution possible is amazing and important when looking at the sub-millimeter-sized anatomy of the coronary arteries.
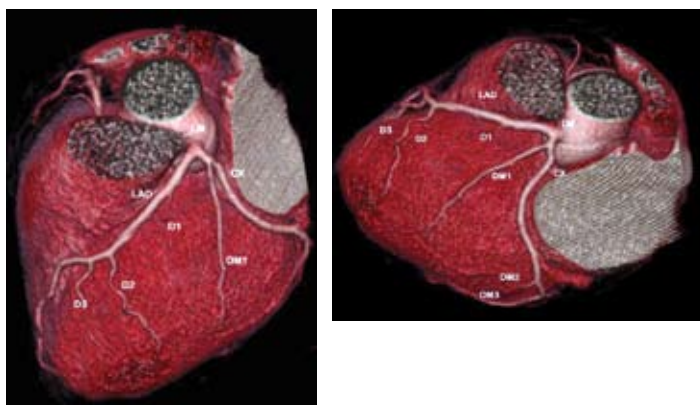
Multi-slice scanners can visualize more than just hard plaque in the coronary arteries. Artery caliber, lumen, course, soft plaque, wall thickness and the presence of dissection, vasculitis, myocardial bridging or aneurysm can be seen by the trained eye. Excellent visualization of the aorta, valves, cardiac chambers and walls, pericardium, and intra-cardiac masses is possible. We think that Cardiac CTA information might supplant that from Echocardiography and Coronary Artery Catheterization in some clinical settings.

The initial image produced in Cardiac CTA is done without contrast and is basically equivalent to EBCT (Electron Beam Computerized Tomography). It gives a calcium score (the importance of this step is explained below). Contrast then is administered through an arm vein to produce an angiogram. The same intravenous site is frequently used to deliver drugs (beta-blockers) to slow the heart rate so that better images can be achieved. The fine resolution gives a very accurate picture. Mollet et. al.[1] show that a negative finding has a predictive value of ~99%, which is higher than can be expected from an exercise electrocardiogram, stress echo, EBCT, or Thallium. Cardiac CTA can effectively exclude or rule out coronary artery disease in the mid-sized arteries, those most amenable to bypass, ballooning or stenting, and most critical to survival.

In terms of risk to the patient, Cardiac CTA is better than coronary artery catheterization. CTA has the huge advantage of being non-invasive, meaning:

• no arterial puncture
• no six-hour bed rest
• no arterial bleeding -- early or late
• no dissection or clot of iliac artery
• no sedation
• no heparin
• no pain
• no triggering dysrhythmia
• no plaque emboli
• no infection
• no stitches

Other significant advantages are that it is quick, takes only about 10 minutes, and can detect both soft and hard plaque. Cardiac CTA can easily visualize graft patency after CABG, which often is impossible via catheterization due to the difficult angles between the grafted and native vessels. Less important, but contributing to the comfort of ill patients, is the fact that the required breath-holding is reduced to only 17 seconds for 16-slice, and nine seconds for 64-slice machines. Another patient-friendly fact is the low expense (approximately $2,000) compared to catheterization (minimum $10,000).

Problem Areas

Although Cardiac CTA has significant advantages, it also has significant problems. Cardiac CTA can't be used if the EBCT score is mid- to high-range because calcium interferes with radiographs. The mineral makes the images inaccurate due to scattering, so the plaque appears to be larger than it is. A good portion of patients who might require coronary artery imaging can be expected to have calcified atherosclerosis

and therefore Cardiac CTA will not work for them—at least not in the arteries that are known to have calcium. If an obstructing lesion is found during a traditional coronary artery catheterization, it can be treated on the spot. This is not possible with Cardiac CTA. It cannot be used with tachycardia, atrial fibrillation, or frequent ectopy because the movement will blur the image. Cardiac CTA does not give a good image of the smaller branches (obtuse marginal, diagonal, septal perforators, etc.).

The disadvantage of contrast use still exists. One must be concerned with possible allergy to iodine or shellfish and the kidney toxicity of cumulative contrast doses, especially in the elderly and people with previous radiation therapy near the kidneys. The radiation dose is higher than with coronary artery catheterization, and is similar to the radiation used for a technetium nuclear stress test. Cardiac patients are at risk for high cumulative radiation exposure.

Given the information above, who are good candidates for the test? A person who is being considered for a catheterization, but whom the attending cardiologist believes is unlikely to need an intervention or for whom he expects to "rule out" coronary disease, is a good candidate. This might include worried asymptomatic people with abnormal lipids, diabetes, or a bad family history, as well as people with atypical chest pain or suspect syndrome X'. Another group would be symptomatic patients with equivocal or discordant traditional cardiac testing, such as: "false-positive" exercise ECG, mildly positive stress ECHO, or diaphragmatic attenuation defects on stress Perfusion scans.

Cardiac CTA could exclude surgical coronary artery disease in the preceding cases and in people with LBBB or other electrocardiographic abnormalities for whom the traditional tests are known to be problematic. It is a very good test to assess graft patency in bypassed patients who have developed symptoms or positive exercise tests. Other excellent candidates for Cardiac CTA are persons needing pre-surgical screening prior to major heart surgery for conditions like congenital anomalies, valve disease, or cardiomyopathy.

The worst candidates would be people for whom an intervention is likely. Poor candidates for the test are those with typical angina, moderately to severely high EBCT scores, people with tachyarrhythmias, and those with very significant atherosclerotic risk factors.

Multi-scanners are fairly new; only about 250 machines exist in the United States. Eight of the top 14 hospitals in the United States, including Johns Hopkins, Mass General, and the Mayo and Cleveland Clinics, have the 64-slice machines. EBCT used to be the only fast, non-invasive way to visualize, albeit indirectly, arterial plaque. Unfortunately, EBCT

has to rely on the correlation of calcium to plaque. Now the multi-slice CT scanners are almost as fast and give far more information. The kind of person who would elect to pay for an EBCT might prefer to pay for a Cardiac CTA. Emergency departments could find that a single, quick Cardiac CTA and cardiac enzymes would allow them to send a lot of chest pain patients home safely and confidently instead of hospitalizing them for observation and more time-consuming tests.

Cardiac CTA Effect on Underwriting

What does Cardiac CTA mean to underwriting? It is a good test. The many cardiac structures visualized were described in the first part of this article. The number, location, and obstructive extent of plaque in the mid-sized vessels would be known and probably rated according to the degree of obstruction per individual company guidelines and philosophy.

Cardiac CTA focuses on anatomy; functional and clinical information is better shown by older tests. For example, it does not give information about the heart's response to exercise or whether an individual gets angina or can achieve high-level performance like a treadmill does. It does not reveal small-vessel disease like a Stress Echo or Perfusion study. It does not show how much of the myocardium is impacted by the compromised vessel in the way that a Thallium does.

Cardiac CTA images soft plaque. It will probably be a good tool for researching the natural history and prognosis of soft plaque. At this time, however, little research data tells us how obstruction by soft plaque compares to that of hard plaque. For now, I recommend looking at the degree of artery obstruction, whether by hard or soft plaque, as roughly equivalent.

As with all of the cardiac tests we underwrite daily, the clinical history, treatment, follow-up, correlation with other test results, and co-morbid factors will impact the use of Cardiac CT Angiogram results in assessing expected mortality.

References

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[2] Other references available on request.

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