2000

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Western University

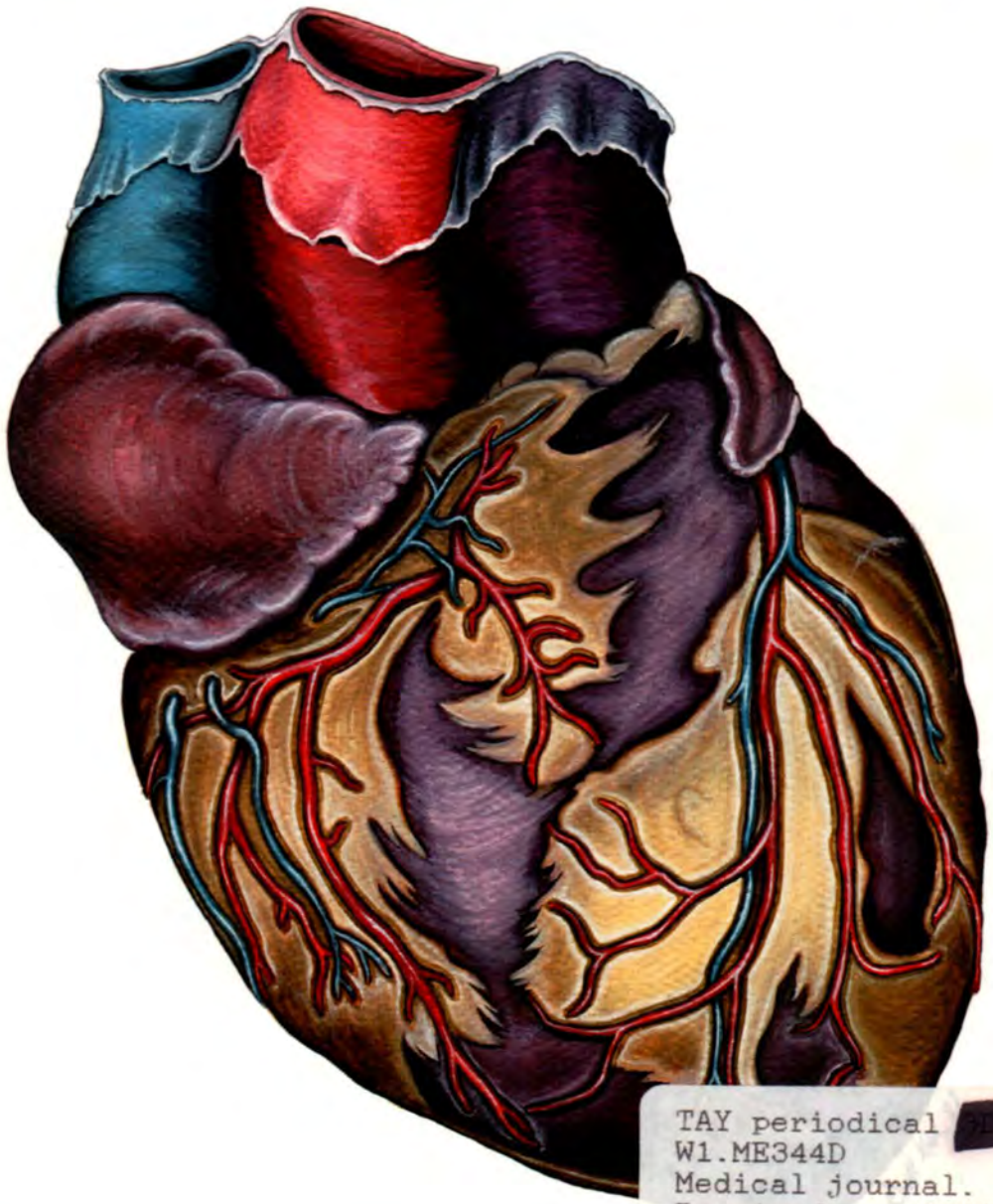
*The* UNIVERSITY *of* WESTERN ONTARIO

# MEDICAL JOURNAL

- An interdisciplinary medical science publication; established 1930 -

Volume 70 Number 1 Spring 2000

# CARDIOVASCULAR MEDICINE



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## THE NEXT ISSUE

## FAMILY MEDICINE

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## COVER ART:

**Scott Kish**

A native of London, Ontario, Scott obtained his degree in Kinesiology from the University of Waterloo, where he specializes in anatomy, and visual information processing. As a self taught illustrator, Scott delivers a unique style of conceptualizing complex information pertaining to the human body in order to attract attention and increase comprehension. His work appears both locally and internationally with clients including doctors, lawyers, advertising agencies, etc.




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Informal peer review is required, i.e., non-specialist authors are encouraged to collaborate with, or at minimum, have their work reviewed for content by a specialist in the field. This individual, if not a co-author, is to be acknowledged at the end of the paper. In addition, it is recommended that all submissions be proof read for significant stylistic or grammatical errors. The editor will not assume responsibility for corrections of this nature and articles requiring such revisions will be returned to the author.

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1. Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992; 339(2):347-50.

2. Dement WC, Carskadon MA, Richardson G. Excessive daytime sleepiness in the sleep apnea syndrome. In: Guilleminault C, Dement WC, eds. Sleep Apnea Syndromes. New York: Alan R Liss, 1978:23-46.


**SUBMISSIONS**

Please direct submissions, including return address, phone and fax numbers, to: UWO Medical Journal, Health Sciences Building, Room MS-175, University of Western Ontario, London, Ontario, N6A 5C1.

Submissions are to include a cover letter, two double-spaced paper copies, and the full text on a 3.5" IBM compatible floppy diskette in Microsoft Word or WordPerfect format. The cover letter should be signed by all authors and indicate that the manuscript has not been published previously.

Short biographical notes on the authors are to be included at the beginning of each paper, on a separate page.

Figures should be professionally drawn; photocopying of illustrations from texts, without the permission of the publisher, is copyright infringement. Each figure, table, or illustration should be submitted on a separate page. Any illustration with a grey-scale should be in the form of a photograph. Two copies of each figure, table, or illustration should be included; each should have its number written on the back, as well as the name of the first author. Legends, which are to be included at the end of the text, should start on a separate page with Arabic numerals corresponding to the figures and tables.

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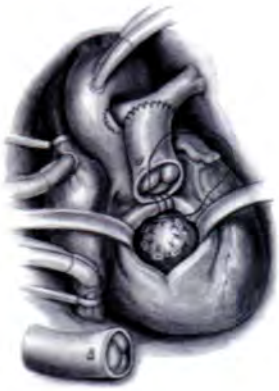

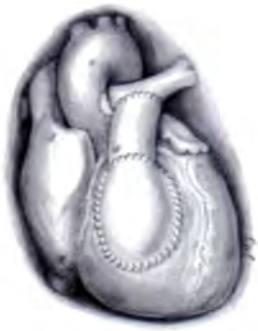

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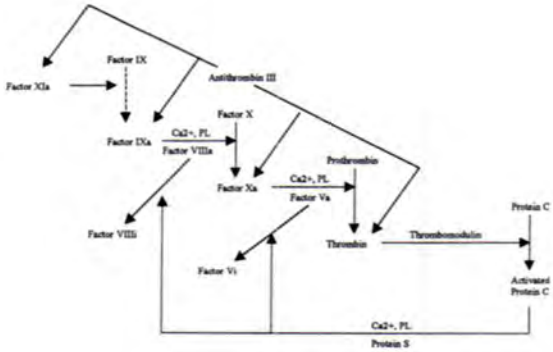


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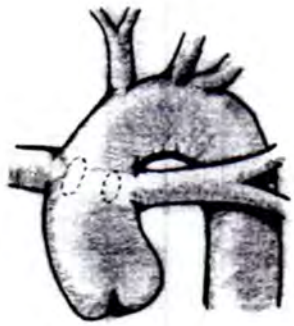

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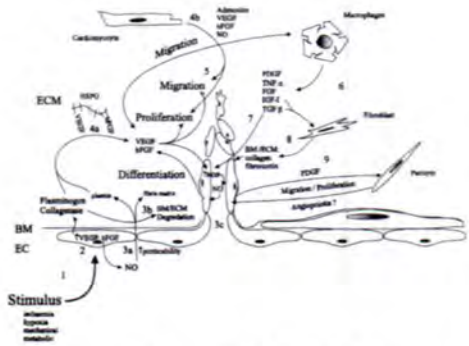



*Therapeutic Myocardial Angiogenesis*

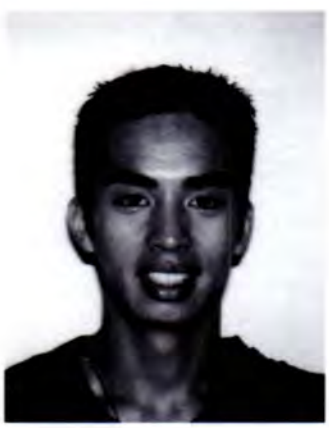
# ABOUT THE EDITORIAL BOARD

**EDITOR-IN-CHIEF**

Dan Hackam is a fourth-year medical student at UWO. He will begin his internal medicine residency on July 1, 2000. Dan has a strong interest in cardiovascular medicine and the determinants of atherosclerosis. He plans to pursue training as a clinician scientist.

**SENIOR ASSOCIATE EDITOR**

Mason Ross is a third-year medical student at UWO. He completed an HBSc in Physiology at UWO, and is currently interested in pursuing a career in a surgical discipline. Mason will be Editor-in-Chief of the UWO Medical Journal next year.



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Eric Wong is a second-year medical student at UWO. He will be Senior Associate Editor of the UWO Medical Journal next year.

# EDITORIAL

## PROGRESS IN CARDIOVASCULAR MEDICINE

*By Dan Hackam, BSc., Editor-in-Chief*

Despite recent declines in mortality, the toll of cardiovascular disease (CVD) in present society is still staggering. CVD accounted for 38% of all deaths in Canada in 1994, more than any other cause of death, including cancer (28%). Twenty-three thousand individuals die each year as a result of a myocardial infarction. Cardiovascular disease costs the Canadian economy approximately $19 billion every year in medical services, hospitalization expenses, loss of income and loss of productivity. With the increase in the proportion of the population that is elderly, the total burden of CVD is expected to rise, at least for the next 15 years.[1]

The term "cardiovascular disease" is a broad one and refers to many different entities, depending on the specialist you speak to, the organ system affected, the age of the patient, whether the disease was acquired or congenital, and so forth. To many, CVD refers to atherosclerosis, which is a spectrum encompassing ischemic heart disease (angina, myocardial infarction, ischemic cardiomyopathy, sudden cardiac death), cerebrovascular disease (stroke, transient cerebral ischemia, vascular dementia), peripheral vascular disease, and arterial aneurysmal disease. Most, but not all, articles in this issue of the journal deal with atherosclerosis.

Medical science has made vast strides in the past half-century towards understanding the underlying mechanisms of cardiovascular disease and innovating new treatments. Epidemiologists, including those involved in the classic Framingham study, have given us an appreciation of the inherent risk factors that contribute to CVD: smoking, hypertension, hyperlipidemia, diabetes mellitus, and age. With the exception of age, these risk factors are largely modifiable: it is likely that public health efforts, focusing on improvements in diet and exercise, are responsible for the dramatic declines in CVD incidence and mortality seen in the past several decades.

In terms of the secondary prevention of vascular disease (that is, the prevention of events occuring in patients with pre-existing disease), clinical investigators have shown us that a multitude of effective pharmacological therapeutics are available, and this has led to much excitement in recent years. Examples include beta-blockers and ace inhibitors for the prevention of death in heart failure patients, statins for the prevention of heart attacks and strokes, warfarin for the prevention of stroke in atrial fibrillation, just to name a few. Unfortunately, this body of evidence is vastly underutilized in much of clinical practice in North America: for instance, one recent study showed that only 27% of hypertensive patients are adequately treated. Here too, then, there is room for improvement.

Diagnosis and therapy of acute cardiovascular events (stroke, myocardial infarction, unstable angina) have also made great leaps in the modern era, giving further credence to the use of the term "progress" in the title of this editorial. The use of radionuclide imaging studies as well as more accurate cardiac enzymes have revolutionized the detection of coronary artery disease and myocardial infarction, respectively. Thrombolytic agents, such as recombinant tissue-type plasminogen activator and streptokinase, have roughly halved the mortality of heart attack patients presenting to hospital. And more revolutionary treatments are on the way: neuroprotective agents for acute stroke, angiogenesis promoters in coronary artery disease, as well as a multitude of other experimental approaches to the problem of myocardial revascularization, techniques which may one day replace coronary artery bypass grafting and angioplasty.

The epidemic of cardiovascular disease in the western world is a real one, with staggering economic and human consequences. One can only hope that scientific advances in the coming century, in combination with better implementation of measures devised in the past century, will usher in the beginning of the end of this modern-day scourge.

*REFERENCES*

*1. Laboratory Centre for Disease Control, 1996.*

Ω

# AN INTERVIEW WITH DR. DOUGLAS BOYD

*By Naji Touma and Helen Lewandowski*

Dr. Douglas Boyd is a cardiac surgeon at the London Health Science Centre – University Campus (LHSC-UC) who has a special interest in robotics-assisted surgery. On September 24 1999, Dr. Boyd and his team performed the first successful closed-chest, robotics assisted beating heart single bypass on John Penner, 60, of Seaforth. This new procedure could revolutionize the world of cardiac surgery and is propelling London's reputation as a world class facility for cardiac research and innovation.

Dr. Boyd received his MD and cardiac surgery training at the University of Ottawa and the Ottawa Heart Institute, respectively. His primary post-cardiac training was in heart transplant surgery and the development of the artificial heart. He was later attracted to London by its world class reputation as a transplant centre. He is currently assistant professor of surgery at the University of Western Ontario and director of the Minimally Invasive Cardiac Surgery Program at LHSC-UC.

**Do you consider yourself a researcher or a clinical surgeon?**

Honestly, I really don't think of myself as a researcher per se. I am a researcher but a clinical researcher. My best work is really done in the operating room. My skills and expertise are in surgery and surgical techniques. Some of these techniques have to be innovated and in order for that to happen, work has to be done in the lab; but the lab work always involves practical models such as studies on animals. I guess I am a researcher but most of my work is clinical. In fact, since I have been here, I would spend four days in the operating room and one day on research. Lately, with this new technology, it is more like two days in the operating room and three days in the lab.

**Could you discuss the technology behind the robotics assisted heart bypass that you recently performed at LHSC-UC?**

We have been concentrating our efforts in minimally invasive surgery lately on beating heart techniques. We know that the smaller the incision is, the more difficult it is to maneuver conventional endoscopic instruments to be able to do the job. Before we knew we were going to be able to use a robot, I went to the lab and used about fifty pig hearts in a training model in order to learn the dexterity required to perform coronary bypass with very small incisions. We learned very quickly that there are a number of problems that have to be overcome before that job can be done. One problem is visualization. The two dimensional camera available at the time did not give us the kind of visual dexterity required. That is when we started experimenting with three dimensional visualization systems. Three dimensional cameras gave us a better perception of depth and improved the visual dexterity. Another problem was stabilization. To operate on the beating heart, one has to be able to locally stabilize the area so that anastomosis could be performed afterwards. Yet another problem was instrumentation. Conventional endoscopic instruments did not allow sufficient degrees of freedom to operate freely within small incisions as in the open heart situation. For example, the ability to move one's hands left and right and look at things freely is reduced greatly. One is also limited by the angle of incision and the distance from the heart to the chest wall. We found that the operation through small incisions is doable but not practical. For example, to do

one single graft, it took us 90 minutes while in the open heart situation, it took us only 10-12 minutes. In addition to the time, the accuracy left something to be desired in that we were not able to obtain the same kind of quality grafts as in the open heart procedure. So there were a number of factors that made us realize it is not quite so easy to perform heart surgeries through small incisions.

All of a sudden, this new robotic technology comes along that would allow the surgeon the same dexterity enjoyed outside the chest with absolute precision. Movements of the surgeon outside are digitized by computer control and translated to a robotic manipulator attached through pin sized holes within the chest wall. The surgeon sits down in front of a control console and manipulates surgical instruments by looking at a magnified TV screen. This view comes from a little 3D camera that is attached to a robotic arm that is in turn hooked up to a computer controller and a headset. The robot supporting the camera is activated by a sophisticated voice activation software that only recognizes the surgeon's voice. The robot only responds to the commands of the surgeon and allows for different camera movements. Hence, the visualization inside the chest is controlled by voice command. The surgeon is sitting at the console, holding instruments very similar to the ones used in open heart surgery. The movements of these instruments are digitized by computer control and transmitted to the instruments inserted within the chest. A surgeon could scale very gross movements on the console to very fine movements in the chest. For example a 6 cm movement outside can be translated to a 6mm movement inside. A surgeon could also move his/her hand from a certain position to a more comfortable position by stepping off a clutch. The computer control also has built-in filters so that very fine tremors are screened out. Another feature is the ability to scale a 180° rotation outside to a 360° rotation inside. Hence, the robot has the effect of increasing a surgeon's dexterity. This is a very interactive system or a robot in the loop that enhances the surgeon's skills but does not take over the operation.

**Could you discuss the benefits of minimally invasive surgery as opposed to open heart surgery?**

There are two factors that make a heart surgery invasive and in turn force patients to stay an average of one week in the hospital after the operation. The first is the incision which is large enough to strip the breast bone and necessitate time for healing. The second is the use of the heart-lung machine. When one takes a patient's blood supply, reroute it into the heart-lung machine (which takes over the functions of both the heart and the lung) and recirculates his blood volume about 20,000 to 30,000 times in this artificial surface, something has got to happen. You never get something for nothing. Things that happen, and they have been very well documented years ago, include: a total body inflammatory response: blood coagulation due to exposure to an artificial surface. The incidence of strokes after heart surgery increases dramatically with age. Our studies have shown that this is largely due to the use of the heart-lung machine; manipulating the blood vessels or having to insert tubes into the aorta. Any manipulation of the aorta causes microemboli that could go to the brain. Microemboli from the pump itself could also go to the brain. Dr. Merken, a professor of anesthesiology, has demonstrated that the use of the heart-lung machine causes a 20-30% increase in neuro-cognitive dysfunction. That being said, there is merit in avoiding the heart-lung machine and invasive surgery.

In minimally invasive surgery, we have not only avoided the use of the heart-lung machine, we have also done small incisions so we don't need to spread an incision about eight inches as in open heart surgery. In fact, one small working port of 2-3 cm long is enough to get the heart stabilized. This enables us to not break any bones and have only a small amount of tissue trauma and ultimately make the surgery a lot more comfortable. This is likely to reduce the need for transfusions and the overall morbidity and complication of the surgery.

**When do you think this new technology will move from the experimental or research stage to become more routine surgery?**

In my own practice now, it is almost routine because I am doing a robotic surgery every week. However, before it is widely adopted, I think it is very important that this new procedure undergoes rigorous scientific evaluation and we have to be very careful before we proceed any further. For example, we do not yet know if these devices are safe. We have been using simple robotics for years and have had no complications associated with the robot whatsoever. We anticipate that this will be the same but until we have an appropriate number of cases, we can't scientifically say it is safe. Once safety is shown, we will be able to demonstrate very clearly the benefits of this technology. After that, we will adopt the robot in routine surgery. I believe that within the next two years, the use of robotics will become mainstream.

**What do you think the limitations of this technology are?**

I think cost is a major issue. This is a very expensive technology. Although, ultimately I believe this technology will pay for itself. We compared low risk patients who underwent robotic beating heart surgery and conventional surgery. Of those 30 patients we looked at, we saved $45,000 by adopting the robotics technology. At this rate, we foresee that our robot will pay for itself within one year. We anticipate that if we can get 24-48 hour stays and patients up and out of the hospital and back to work quickly, this technology will pay for itself; but right now, the cost is the greatest limiting factor. This technology is in a rapid state of evolution. I don't think the unit we have now will be the same unit used two years from now. We currently have contracts with a private company that we will be involved in helping them develop their instruments. In return, we will get upgrades in the equipment in order to stay up to date.

**Other than the bypass, do you foresee using this technology for other types of surgery?**

Absolutely, there is no question about that. I believe very strongly that in the next two years, we will be doing beating heart robotic valve replacements, robotic

arrhythmia operations and even pediatric surgery.

**Could you discuss the genesis of this technology and how it developed?**

Robotic research really started in the early 90's. There were two major groups in California working on it independently. One was the US military with the Stanford Research Institute and the other was NASA and the Jet Propulsion Lab. These two groups had different objectives.

The goal of the military group that contracted out to the Stanford Research Group was to have a robotic manipulator on a bunker like tractor trailer. The idea was to have the ability to move wounded soldiers quickly into this portable hospital with robots and have surgeons on their command console performing surgery from miles away. With the advent of fiber optics technology, data transmission could be done almost at the speed of light.

The objective of the group at the Jet Propulsion Lab of NASA was to have a robot on a mission to Mars where astronauts could go for two years without a hospital. The idea was to have a technician deploying the robot on board of the spacecraft and have a surgeon on earth perform any potential surgeries. This idea is not so far fetched and there is no question in my mind that this will be something available within seven years.

**Could you talk about how important private funding such as the Ivey Foundation gift is for maintaining and developing this research technology?**

Right now, I think we have established ourselves as a major robotic surgery centre in the world. One of the obligations we have is to further robotic surgery and if we are going to do that in a scientific way, we have to have the foundations. The additional money from Ivey will not only support our research efforts but also our clinical efforts. Just having a robot will not make us a world class facility; we need research, teaching and clinical applications. This generous Ivey gift will help in laying down these foundations. It will not only fund the robotic program but also the imagery program. It will enhance our ability to link robotic surgery and interventional cardiology. This will make London a leader in the world in this minimally invasive approach to heart disease.

**Could you discuss other important current issues in cardiology and cardiac surgery?**

There is no question that angiogenesis and the whole issue of genetic research plays an important role. Also, stem transfer technology or the ability to transfer heart muscle cells into dead areas and regrowing it. Other important research areas include: myocardial revascularization, cardio-laser revascularization in association with genetic manipulation, robotics, catheter-based interventions, and endocardioly or ethocardioly.

**What would you tell medical students who may be interested in pursuing cardiac surgery as a career?**

Cardiac surgery is an extremely demanding but also an extremely rewarding career. This is really an exciting time to be a cardiac surgeon. Heart surgery has been practiced the same way for almost 30 years. In the last few years, even while I was undergoing my cardiac surgery training, it is being completely changed. Right now, we are about to redefine the way cardiac surgery is practiced and that is really incredible. The advent of things like computers, genetics and robotics have greatly impacted on cardiac surgery and that is very exciting. Ω

# THINKING ON YOUR FEET

*EDITORS: ALLAN VESCAN AND JOHN LEE*

## AN UNUSUAL CASE OF CHEST PAIN

*By Dan Hackam, BSc., Editor-in-Chief*

A 45-year old gentleman (A.B.) presents to his family physician with a 24-hour history of severe chest pain. The pain is localized to his left anterior chest, is sharp and stabbing in quality, and was fairly sudden in onset and has not remitted since yesterday. The pain is worse with recumbency, cough, and deep inspiration, and better with sitting up and taking shallow breaths. A.B. took aspirin with only moderate relief.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS:

1) What is your differential diagnosis for chest pain in this gentleman?

2) What other questions on history would clarify the differential diagnosis?

3) Given the most likely diagnosis, what particular finding on physical examination would you be diligent to seek out?

Examination of the head and neck, abdominal, respiratory and musculoskeletal systems is unremarkable. Turning your attention to the cardiovascular system, you obtain the following parameters: HR 100 and regular, BP 140/70, JVP 3 cm above the sternal angle. Carotids are brisk bilaterally with no evidence of bruit. On inspecting the precordium, you note no abnormal lifts, heaves, or pulsations. On palpation, there is no parasternal lift and the apex beat is located in the fifth interspace, midclavicular line (it is normal in timing, duration and intensity). On auscultation, you note normal heart sounds, a Grade II/VI systolic ejection murmur at the base with no radiation to the carotids, no extra heart sounds, and no rub.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS:

4) If a carotid bruit were present, what would this indicate, and what clinical entity on the differential diagnosis would this make more likely?

5) What is the significance of a parasternal lift? What would a displaced apex beat tell you?

6) What is the significance (if any) of the murmur?

7) What initial investigations would you order?

CBC reveals a left-shift with mild leukocytosis (WBC 11.3) and a neutrophilic predominance. Cardiac enzymes (myoglobin, troponin-I, CK-MB) and ESR are mildly elevated. A resting electrocardiogram (ECG) reveals the following: normal sinus rhythm, rate 98, ST elevation in multiple contiguous leads. Chest X-ray reveals a normal heart size with no evidence of pleural effusion or pulmonary infiltrates.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS:

8) Given the abnormality on ECG, what diagnosis is most likely?

The patient is referred to a cardiologist for further assessment. Echocardiography (ECHO) reveals evidence of a mild pericardial effusion, with no evidence of pericardial thickening, valvular abnormality, or dyskinetic myocardial segments. Ejection fraction is 55%.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS:

9) What are the etiologies of this condition?

10) What is the prognosis of this condition?

11) Outline, in general and specific terms, the management of this condition?

ANSWERS:

1) One can never be faulted for placing at the top of the differential those entities that might endanger the life of the patient, and therefore must be ruled out. Given the sudden onset of severe chest pain, myocardial infarction or ischemia, aortic dissection, or pulmonary embolus are all possible. However, **pericarditis** is more likely, given that the pain of acute pericarditis is often pleuritic, relieved by sitting up and aggravated by recumbency and deep breathing.

2) The four cardinal cardiac symptoms are: chest pain, dyspnea, palpitations and syncope. In addition to these, one would ask about symptoms of heart failure: orthopnea, paroxysmal nocturnal dyspnea, and ankle swelling. Chest pain related to exertion, emotion, cold weather or meals, or in the presence of diaphoresis, nausea, or vomiting, or against a background of coronary risk factors (smoking, hypertension, diabetes, family history,

and hyperlipidemia) make infarction/ischemia more likely. One would also ask about habits such as tobacco and ethanol consumption, as well as medications, and other medical conditions (for instance, lupus [SLE] and other connective tissue disorders are associated with pericarditis).

3) The *sine qua non* finding of pericarditis is the **pericardial friction rub**. It may have up to three components per cardiac cycle and is high-pitched, scratching, and grating; it can sometimes be elicited only when firm pressure with the diaphragm of the stethoscope is applied to the chest wall at the left lower sternal border. It is heard most frequently during expiration with the patient in the sitting position. The rub is often inconstant and the loud to-and-fro leathery sound may disappear within a few hours, possibly to reappear the following day.

4) A carotid bruit indicates turbulent flow in the carotid artery and is diagnostic of cerebral vascular disease. Because atherosclerosis is a generalized disease, the finding of a carotid bruit would make coronary ischemia or infarction somewhat more likely.

5) A parasternal lift is palpated in right ventricular hypertrophy. A displaced apex can be found in left ventricular dilatation.

6) The murmur described has all the characteristics of a benign ("functional") flow murmur, which is often seen in healthy, young adults and in high-flow states such pregnancy, exercise, and anemia. These characteristics are: midsystolic timing, Grade II or less, non-radiating, best heard in the pulmonic area, non-musical in character.

7) The following investigations are appropriate: complete blood count (CBC), erythrocyte sedimentation rate (ESR; a non-specific marker of inflammation), cardiac enzymes, electro-cardiogram, and chest x-ray.

8) Pericarditis.

9) Differential: infectious (viral, bacterial, tuberculous, fungal, protozoal), associated with myocardial infarction (actuely, or days to weeks later; the latter is known as Dressler's syndrome), collagen vascular disease (SLE, periarteritis nodosa, rheumatoid arthritis), uremia, neoplasm (breast, lung, renal, melanoma), infiltrative disease, drugs, trauma, radiation, and idiopathic.

10) The prognosis is dependant on the underlying etiology. Acute idiopathic (or viral) pericarditis is usually self-limited and abates within 1 month. One or more episodes of recurrent pericarditis occur in up to one-fourth of patients. Constrictive pericarditis is a rare complication.

11) The treatment of pericarditis is virtually always symptomatic and directed towards optimizing the comfort of the patient. Bed rest and anti-inflammatory treatment with aspirin, if necessary up to 900 mg qid, may be given. If this is ineffective, one of the nonsteroidal anti-inflammatory agents, such as indomethacin (25 to 75 mg qid) or a glucocorticoid (e.g., prednisone, 20 to 80 mg daily) usually suppresses the clinical manifestations of the acute illness and may be useful in patients in whom the purulent and tuberculous forms of pericarditis have been excluded. Anticoagulants should be avoided. After the patient has been asymptomatic and afebrile for about a week, the dose of the anti-inflammatory agent is gradually tapered. When recurrences are multiple, frequent, disabling, and continue beyond 2 years, pericardiectomy may be effective in terminating the illness. Ω

# DEFECTIVE PACEMAKERS AND LEGAL LIABILITY

By Mahmoud Sharaf, MEDS 2002

With the development of pacemakers and implanted defibrillators, patients prone to cardiac arrhythmia by reason of ischemic disease or congenital abnormality have seen dramatic improvement in quality of life and life expectancy. The pacemaker consists of an external unit, either single or dual-chambered, with a lead embedded in the right atrium, or two leads implanted in atrium and ventricle[1]. The pacemaker sets the heart rate and can adjust dynamically to suit systemic activity levels[1].

The combination of intense patient reliance on these devices to sustain an active lifestyle and the inevitable tendency of mechanical parts to malfunction can result in cardiac events, and even death. The courts are a frequent recourse for settlement of claims of manufacturer liability for the complications of pacemaker malfunction. There are several actual and potential claims that plaintiffs can use. This paper will serve to discuss a few of them using illustrative examples.

In the case of *Tracy v. Telectronics Pacing Systems, Inc.*, Ronald Tracy of St.Clair County, Michigan brought forth a lawsuit against the manufacturer after his pacemaker failed, forcing him to replace it at the Cleveland Clinic at substantial personal risk and expense[1]. The J-lead pacemaker has a thin, flat intracardiac lead that is abnormally prone to metal fatigue, thereby incapacitating the pacemaker. The proceedings in the U.S. District Court indicated the manufacturer was aware of the fault as early as 1992, but did not recall the unit until 1994, a year before this trial[1]. The court decided in favour of the plaintiff1. The Food and Drug Administration ascertained from Telectronics, Inc. that 22 000 persons have received the J-lead model which the company estimates has a 17% failure rate[1]. It is estimated that 2 individuals have died as a result of this malfunction[1]. There are currently 60 pending cases against Telectronics Pacing Systems, Inc. in U.S. courts[1].

In Ontario there are 2 cases pending against Medtronics, Inc.'s Canadian subsidiary, out of Mississauga[1]. In 1998, Sudbury residents brought a class action suit against the company because of faulty polyurethane insulation on the leads. Any of the thousand Ontarians having received the 4004 model (between 1989-1995) is eligible to participate in the suit[1].

Susan and Jeff Blanchard of London, Ontario brought forth a suit in November, 1998 in the Ontario Court of Justice against the same manufacturer of the 4004 model alleging negligence in the design, development, testing, manufacture, licensing and distribution of their product. They seek $275 000 in assorted damages[1].

The risk of serious atrial thrombus formation pursuant to pacemaker lead implantation is rare (only about 2%)[1]. However, the possibility of claims being drafted based on thrombogenic lead configuration can not be discounted.

Another interesting potential cause for future claims is the proposed link between cellular phone use and interference in pacemaker signaling. The New England Journal of Medicine study (May 29, 1997) indicated that if cellular phones were operated directly over the precordium, interference could be noted in 20% of individuals. Serious interference was noted in one third of this twenty percent. Normal operation of cellular phones at ear level had no role in producing interference[1]. There have been no cases to date brought to general attention that have been argued along these lines, but this may not dissuade enterprising lawyers from trying.

The last, and perhaps most interesting, potential cause of lawsuits in the future is the Y2K non-compliance issue. This *cause celebre* of Ann Couffou, Managing Director of the Giga Year 2000 Relevance Service, was serious enough to warrant her testimony before the House Subcommittee on Science and Technology in 1997[1].

The Veterans Administration asked 5 pacemaker companies about Y2K readiness. One company refused outright to cooperate while the other four indicated readiness would be achieved before the end of 1999[1].

In actuality, most pacemakers (including those made by Medtronic, Inc. and PaceArt, Inc.) have no date-computing chips, and are thus Y2K-proof[1]. Some pacemakers contain chips that serve to record cardiac traces for physicians to study. These date-computing chips would cease to record information on New Year's Day, and thus will sacrifice the close monitoring required in some patients[1]. Implanted defibrillators, which assess arrhythmia and rectify it, do use date-computing chips. If these monitors have recorded no event in 6 months time, then the defibrillators will not subsequently function, assuming the long inactivity means that the device should be replaced because it may be defective. If no event has been recorded since 1900 (which is the case on 01.01.2000), then the defibrillators will stop, not in line with replacement schedules[1].

Some manufacturers of date-computing chips have switched to an 8-digit date format to avoid Y2K problems, like the British manufacturer of CriSP[R]. Others are still considering the problem[1].

In conclusion, the grounds for successful liability suits for pacemaker malfunction will primarily rest on demonstration of mechanical defect present at production or abnormal tendency to wear out. It is important to show

multiple cases of malfunction for the model in question. The technology of pacemakers has greatly improved over the decades and lawsuits, despite their unsavoury connotations, have played an integral part in the continuous drive towards product quality and standardization.

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Ω

# A BRIEF REVIEW OF TRUNCUS ARTERIOSUS

By John D. Stein and Jason Ashley

## INTRODUCTION

Truncus Arteriosus, first described in detail in 1798, is a congenital defect of the great vessels involving incomplete separation of the pulmonary artery and the aorta during embryogenesis. The condition affects 1 in 12,500 births[1] and patients present with cyanosis, tachypnea (very rapid ventilation), murmurs, sweating during feeding, a failure to thrive and hepatomegaly[1]. Other anomalies associated with TA include ventricular septal defects, truncal valve regurgitation and increased pulmonary vascular resistance[1]. Untreated, this condition has a 65% mortality rate in the first 6 months of life increasing to 75% within the first year[1]. Causes of mortality include excessive pulmonary blood flow, congestive heart failure and progressive cyanosis due to accelerated pulmonary vascular obstructive disease. Palliative surgical intervention performed before these conditions appear has lowered the two-year mortality to approximately 20%.[1]

### Embryology and Etiology

In the normal development of the great vessels, truncal ridges form in the truncus during the fifth and sixth weeks of embryogenesis. The left anterior ridge meets and fuses with the right posterior ridge (Fig. 1) during the seventh week of gestation thus forming two lumen which give rise to the aorta and pulmonary artery. The fusion of the truncal ridges also occurs in the fetal heart contributing to ventricular septum formation. The failure of these ridges to fuse has been used to explain Truncus Arteriosus, and by extension, the observed ventricular septum defects.[1] This model of development has been accused of being an oversimplification and not fully accounting for the possibility of Truncus Arteriosus without a ventricular septal defect.[1] Admittedly however, this occurrence is exceedingly rare with only 2 documented cases.

Truncus Arteriosus is frequently associated with DiGeorge's Syndrome, a condition where the thymus and parathyroid glands fail to develop from the neural crest. Ablation of the cardiac neural crest in chick embryos has been shown to result in persistent Truncus Arteriosus. A theory that the etiology of Truncus Arteriosus may involve some genetic defect or teratogenic insult affecting the neural crest may explain the frequent association of these two congenital malformations.[1] This is an attractive idea since any damage to the neural crest that would compromise truncal ridge fusion could have the potential of also interfering with the normal development of the thymus and parathyroid glands.

### Anatomical Classification of Truncus Arteriosus

At present there are two main systems for classifying Truncus Arteriosus. The first, introduced in a classic report by Collett and Edwards in 1949[4] was widely adopted. In general the defect was classified according to the arrest in development which corresponds to the position of pulmonary branching from the truncus. (Fig. 2)

Type I. Type I involves a short pulmonary trunk which further divides into a left and right pulmonary artery. This type is further subdivided into 7 categories (Table 1).

Type II. In Type II Truncus Arteriosus the right and left pulmonary arteries have separate but close origins from the dorsal wall of the Truncus Arteriosus. This type is further subdivided into 4 categories (Table 2).

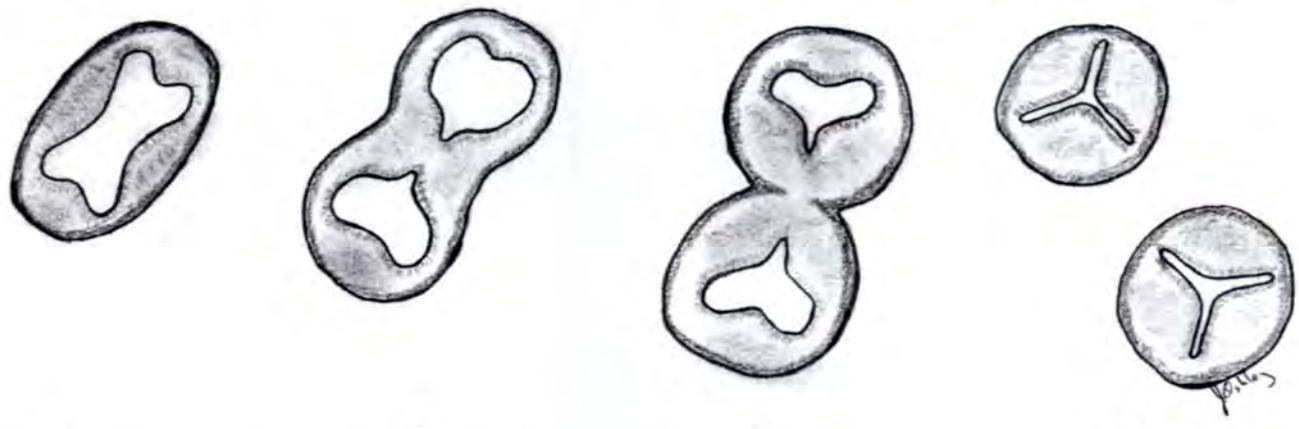


***Figure 1.*** *Embryogenesis of the Aorta and Pulmonary Arteries arising from the Truncus Arteriosus at the 5th (**A**), 6th (**B**), 7th (**C**), and 8th (**D**) week of gestation.*

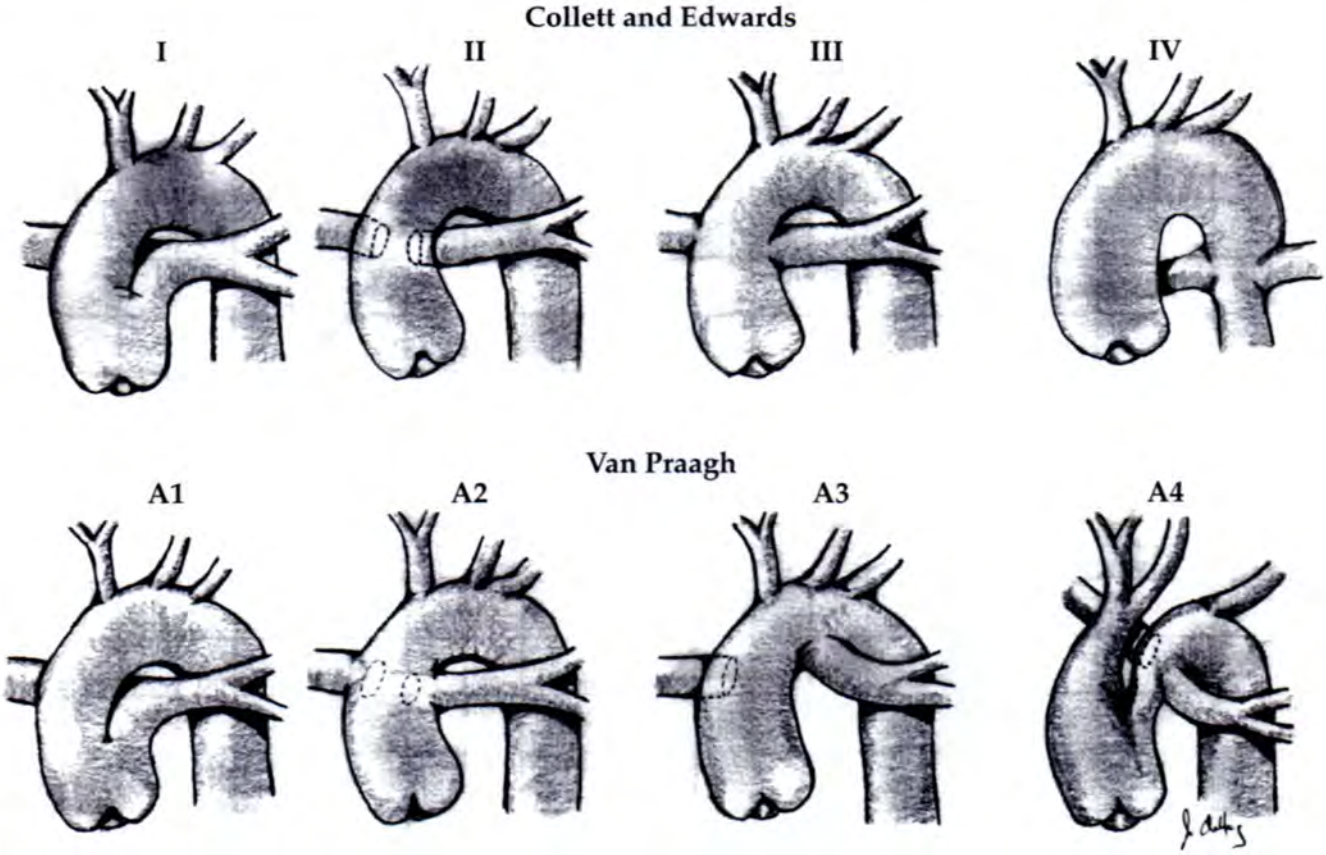


*Figure 2. A comparison of the Collett & Edwards and Van Praagh & Van Praagh Classifications of Truncus Arteriosus.*

Type III. In type III Truncus Arteriosus the right and left pulmonary arteries have separate origins from the right and left lateral walls of the truncus. This type is further subdivided into 4 categories (Table 3).

Type IV. Type IV Truncus Arteriosus is characterized by an absence of pulmonary arteries as well as a lack of any 6th aortic arch derivatives. Perfusion of the lungs occurs by way of the bronchial arteries. Type IV is further subdivided into 4 categories (Table 4).

An alternative classification system was offered by Van Praagh and Van Praagh[7] to include instances of Truncus Arteriosus *without* ventricular septal defects (VSD) and further, to exclude Collett and Edward's Type IV category. It was argued that Type IV should be considered a case of failed pulmonary artery formation rather than a failure of the aorta and pulmonary artery to separate.

**Table 1**

| | |
|---|---|
| Type I | Single pulmonary trunk arising from the Truncus Arteriosus (from the left side unless otherwise noted) |
| Subtype 1 | Pulmonary trunk from left side. |
| Subtype 2 | Pulmonary trunk from right side. |
| Subtype 3 | Patent ductus arteriosus. |
| Subtype 4 | Patent ductus arteriosus and coarctation of the aortic arch. |
| Subtype 5 | Complete atresia of part of the aortic arch. |
| Subtype 6 | Right aortic arch. |
| Subtype 7 | Double aortic arch. |

**Table 2**

| | |
|---|---|
| Type II | Separate but close origins of the right and left pulmonary arteries |
| Subtype 1 | Ductus arteriosus is absent. |
| Subtype 2 | Patent ductus arteriosus. |
| Subtype 3 | Patent ductus arteriosus with coarctation and atresia of the aortic arch. |
| Subtype 4 | Right aortic arch |

**Table 3**

| | |
|---|---|
| Type III | Separate origins of the right and left pulmonary arteries from the right and left lateral wall of the truncus. |
| Subtype 1 | Ductus arteriosus is absent and both 6th aortic arches present. |
| Subtype 2 | Patent ductus arteriosus with only one 6th aortic arch present and supplying one lung. The other lung perfused by the ductus arteriosus or bronchial arteries. |
| Subtype 3 | Right aortic arch and both 6th aortic arches present. |
| Subtype 4 | Right aortic arch with only one 6th aortic arch present and supplying one lung. The other lung perfused by the ductus arteriosus or bronchial arteries. |

**Table 4**

| | |
|---|---|
| Type IV | Pulmonary arteries are absent |
| Subtype 1 | Bronchial supply to lungs via descending aorta. |
| Subtype 2 | Bronchial supply to lungs via descending aorta and aortic arch. |
| Subtype 3 | Bronchial supply to lungs via aortic arch. |
| Subtype 4 | Right aortic arch and bronchial supply to the lungs via descending aorta. |

**Table 5**

| | |
|---|---|
| Type A | Truncus Arteriosus with VSD |
| Subtype 1 | Partial separation of a main pulmonary artery from the truncus. |
| Subtype 2 | No main pulmonary artery, right and left branch off from the truncus separately. |
| Subtype 3 | Absence of single pulmonary artery (left or right). Ipsilateral lung receives collateral perfusion. |
| Subtype 4 | Atretic or absent aortic arch with large patent ductus arteriosus. A main pulmonary artery arises from the ascending aorta. |

**Table 6**

| | |
|---|---|
| Type B | Truncus Arteriosus without VSD |
| Subtype 1 | Partial separation of a main pulmonary artery from the truncus. |
| Subtype 2 | No main pulmonary artery, right and left branch off from the truncus separately. |
| Subtype 3 | Absence of single pulmonary artery (left or right). Ipsilateral lung receives collateral perfusion. |
| Subtype 4 | Atretic or absent aortic arch with large patent ductus arteriosus. |

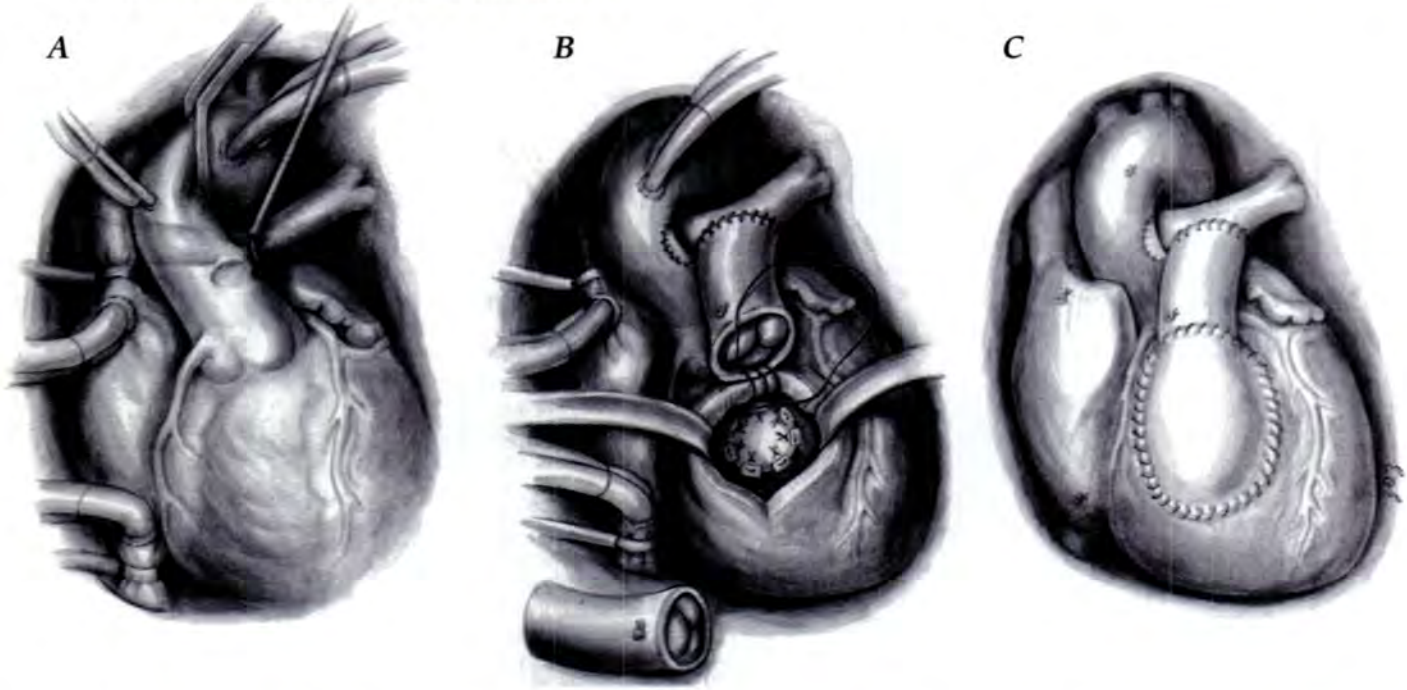


***Figure 3.*** ***A.*** *Truncus Arteriosus with aortic cross-clamping, pulmonary artery constriction, and aorto-bicaval bypass in place.* ***B.*** *Transventricular closure of the ventricular-septal defect using a Dacron Patch has been performed. The pulmonary trunk has been excised from the truncus. The resulting neoaortal defect is closed with a homograft patch. The pulmonary trunk is sutured to a homograft conduit which is in turn sutured to the rim of the ventricular defect.* ***C.*** *In cases where the pulmonary artery graft cannot envelop the entire ventricular defect, an homograft hoot may be implemented. 3/4 of the hood circumference is sutured around the remaining rim of the ventricular defect. The pulmonary artery is sutured to the remaining 1/4 of the hood's circumference to complete the continuation between the pulmonary artery and the right ventricle.*[2]

In their scheme, Van Praagh and Van Praagh classify Truncus Arteriosus with ventricular septal defect as Type A. (Fig. 2) The exceedingly rare occurrence of Tuncus Arteriosus without ventricular septal defect occurs when the pulmonary infundibulum develops normally as do separate pulmonary and aortic valves. Within the trunk however, there is a defect in the septum which would normally separate the aorta and main pulmonary artery such that there is direct communication between the two and mixing of oxygenated and deoxygenated blood. Van Praagh and Van Praagh classify this type of Truncus Arteriosus as Type B. These two broad categories are further subdivided as outlined in tables 5, 6.

Given the variable morphology of this condition, a review of each procedure devised for each subtype is beyond the scope of this review. Instead, a description of the latest procedure for addressing the most common form of Truncus Arteriosus will be undertaken.

**Repair of Truncus Arteriosus Type I-1 / A1**

The goal of the procedure to repair Truncus Arteriosus Type I-1 / A1 is to restore, as nearly as possible, the regular course of blood flow from the heart to the lungs and systemic circulation. To begin, the patient is put on pediatric cardiopulmonary bypass ( Fig 3-A) which may also include deep hypothermic circulatory arrest to extend the time the patient can be sustained on bypass.[1,2,3,4] The pulmonary trunk is divided from the Truncus Arteriosus and the resulting defect, in what is now the neoaorta, is closed.

To correct any regurgitative flow diagnosed pre-operatively, repair of the truncal valve would be indicated prior to closure of the neoaorta. This involves removing the smallest valve leaflet (usually one of four) and closing the incision to bring separated leaflets into close approximation.[1] The ventricular septal defect is approached through a right ventriculotomy, and closed

with an albuminized Dacron or Gortex patch (Fig 3-B).[5] The excised pulmonary artery is fashioned into a tube with the aid of an allograft patch if necessary (Fig 3-B). The pulmonary trunk is then sutured to the right ventricle at the site of the ventriculotomy (Fig 3-B). This final communication may implement a non-valved Dacron conduit[1] or a valved homograft. If the graft is unable to completely surround the ventricular defect a homograft-pericardial hood may be implemented to channel blood flow from the ventricle and into the pulmonary artery (Fig 3-C).

**Post-Operative Mortality**

The morbidity associated with the repair of Truncus Arteriosus has certainly been reduced with recent technological innovations that improve the surgeon's ability to maintain an infant on cardiopulmonary bypass. However, one of the most significant factors contributing to a reduction in mortality for repair of this condition is the indication that such repairs be performed before the patient reaches six months of age.[5,11,1] In this way, a significant contributor to early death, pulmonary morbidity due to protracted pulmonary hypertension, can be preempted with early repair of the defect.

While a patient age of less than six months of age is desirable for reducing mortality, more stringent requirements may be necessary for minimizing morbidity. Hanley et al. reported that morbidity, as indicated by pulmonary hypertension, was increased by postponing surgery beyond 1 month of age.[11] While not an immediate contributor to death, Hanley et al. suggest that "...an intensive care unit team with less experience managing pulmonary vascular problems could theoretically increase the significance of this factor as a risk for death."[11]

The age of the patient has been demonstrated to greatly improve intermediate survival. For repairs performed on infants less than 30 days old, survival at 1 month has been reported at 87% and 81% at 3 months and beyond[5]. Hanley et al. reported 83% of patients surviving to 4 months post-operatively and as many as 76% surviving to as late as 22 months post-operatively.

**Conclusion**

Truncus Arteriosus is a rare cardiac congenital defect. While the mortality rate of the condition is very high in the untreated infant there are procedures to repair vessel architecture which have promising rates of success. The opportunity for a favourable outcome is maximized with early intervention as the sequelae of pulmonary hypertension and the associated pulmonary morbidity can be mitigated or eliminated.

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# TAOISM AND THE ADVENT OF ANCIENT CHINESE MEDICINE

*By Vadim Sherman*

A retrospective view of civilization has shown that scientific advancement of a society can only take place if the social infrastructure allows for it. Ancient China was no exception in that the structure of society and the conditions of the time were such as to allow for advancements in medicine. More specifically, ancient Chinese society fostered the Taoist religion, thereby allowing Taoist followers to pursue their ultimate goal of immortality, thus indirectly advancing medical knowledge, mainly in the field of pharmaceutics.

Society was capable of fostering the ideas of Taoism since the underlying beliefs that Chinese society prescribed to paralleled the paradigms of Taoism. These beliefs were centred around the doctrine of Yin and Yang, in which Nature was a single, unified system with polar and complementary aspects. When they are in balance, life is harmonious. However, when the delicate balance is upset, disaster looms[1]. The first followers of Tsou Yen's philosophy merged with the Taoists, who then adopted Tsou Yen's ideas[2]. Furthermore, the aspect of Taoism that dealt with the search for immortality had originated from folk medicine[3]. Thus, since the Taoist religion conformed to prevailing ideas held in the culture, such as that of Yin and Yang, and was born of the magico-religious part of society, Taoism was able to progress within the society generally unabated.

Another parallel between social attitudes and Taoism that allowed it to flourish was that both were concerned with the idea of prevention. In ancient times, China was a bureaucratic feudalism where great importance was attached to the prevention of trouble both in politics and in personal health[3]. As the term bureaucracy implies, there would be little imagination on the part of government employees to solve problems since they would all be dealt with in a preordained mechanistic fashion. This then necessitated a need to prevent potential problems from ever arising. Prominent members of society, such as Emperor Hsia Tzu-Liang, established the first permanent hospital in 491AD. Before such time, hospices had been formed only in times of locust plague, severe drought or other types of epidemics[3]. This action, on the part of the Emperor was most probably due to the prevailing attitude of prevention present in ancient China. Taoism mirrored this basic principle in their philosophies of immortality[4]. By searching for immortality, the Taoists were concerned with keeping the health of the individual so as to prevent the occurrence of any disease which could potentially lead to death.

By being devout Taoists, many monks were able to advance their social standings by rising to positions in the Emperor's court. Since their philosophies were favored by the ruling class, the religion was free to develop. Their escalation through the social hierarchy was facilitated by the desire of Emporers to drink the formula of life. To fulfill this desire, they enlisted the knowledge and scientific skills of the Taoists, and with it came the open support of the religion. The fascination Emperors had with Taoist beliefs of immortality is reflected in a preface to one recipe for the elixir. It describes the Yellow Emporer's journey to the Taoist Chung Huang-chih to tell him that he is giving up his place on the throne to pursue Tao (the order of things)[5]. The Taoist philosophy was a strong current under a great number of rulers, especially from the First Emperor onwards through the Han dynasty. The Taoists were favored by rulers to the point that their religion was actively furthered.

One such ruler, Thopa Kuei, instituted a professorship of Taoism and alchemy with facilities for the study and preparation of elixirs[3]. The Mongols, like Thopa Kuei, were also very receptive to various Taoist practices[6]. For instance, in 1276, Khubilai issued an edict in which he summoned the head of the South Taoist clergy to Shang-tu from whence they had a formal spokesman in the capital. From this point on and until the end of Mongol rule, Taoism held a major position in the religious lives of the rulers and the Taoist influence was there in the court and government. The influence Taoism exerted upon the court was evidenced strongly between the years 1307 and 1322, when on many occasions there were edicts issued that demanded the protection of the Taoist religion[6]. The Taoists were very capable of attaining influence in the ruling section of society and with this influence the Taoist philosophy was further fostered.

With this fostering by the court and their political influence as seen in Mongol times, it is obvious that the religion was anything but persecuted. As long as the religion is not persecuted by the ruler, it is allowed to flourish and thereby attempt to achieve its goals. Alchemy was the main occupation of the Taoists and it flourished during the Mongol rule[6]. It was through these alchemical practices that the pharmaceutical knowledge of ancient China developed.

**ABOUT THE AUTHOR**

*Vadim Sherman is a fourth-year medical student with an interest in the history of medicine. He is also the recipient of 1996-1997 Rowntree Prize in Medical History.*

A consequence of the Taoist search for immortality was that many recipes for the elixir of life were created, which amounted to a wealth of knowledge about "life-prolonging drugs". Although many of these elixirs proved to be impotent, this does not detract from the fact that due to Taoist work in alchemy, the amount of experimentation increased, leading to the increased knowledge of drugs in general. One of the things that Taoists living in solitude occupied themselves with was the writing of compendiums of pharmaceutics. These became known as the Pen-ts'aos[7]. The descriptions of elixirs were followed with Taoist monks' to insights and experiences on how to achieve long life without aging. The Taoist Ma Chih compiled a collection of drugs by adding another 133 types to the repertory of the Pen-ts'ao, which were used then and now as successful prescriptions[7]. In another of the Pen ts'aos, one of the many recipes for immortality includes sulfur, which found use later in civilization as an antidote to arsenic poisoning[7].

The use of sulfur was one of many successful drugs and recipes that came into use through the experimentation of Taoist alchemists. There were many more, one of which was ammonium chloride. Medically, it was used to stimulate expectoration. It was introduced by Arabs, who had picked it up from their Chinese alchemical colleagues[8]. Moreover, T'ao Hung-ching, another Taoist alchemist, was quick to observe through his alchemical experiments that mercury was able to change gold and silver into a paste. It turned out that he had discovered the principles of amalgams and this was to have an effect on health care since these amalgams were then used for filling teeth[7].

Taoists also dabbled in iatro-chemistry, leading to further advancements in medicine. By preparing mixtures of androgens and estrogens in a relatively purified form, they were able to treat many hypo-gonadic conditions. This advent of medicine had come about since sexual endocrinology and special sexual practices had always been one Taoist method of attaining immortality[3]. Evidently, Taoism has made a distinctive mark on medicine through constant experimentation and development of new therapies.

Most of Taoist success in medicine was seen in pharmacopoeias, where the Taoist philosophy led to more works and expansion of works on drug literature. One author of the pharmaceuticals, T'ang Shen-wei, combined the Chia-yu pu-chu Shen-mung pen-ts'ao and the T'u-ching pen-ts'ao into a single work that was more practical for the practitioner. He also inserted an additional 662 treatises of drugs and expanded the complete work by approximately 29,000 instructions for drug applications. He did not write into the books any of his own views, but instead quoted from other authors and referenced other material. Nine of those references pertained to other Pen-ts'aos, 89 were from other medical literature, one from a Buddhist work, and 35 were from Taoist works[7].

The way in which the ancient Chinese society can be viewed then, is as a cyclical arrangement. One can start by saying that Taoist experiments in alchemy led to advances in drug knowledge and other general fields of medicine. However, this would not have been possible, were it not for the fact that society, on all levels, fostered the development of Taoism, thus allowing it to pursue its goals with the utmost freedom. With this freedom, then, the Taoists were able to influence society into subscribing to their philosophies, inspiring them to make medical advancements with Taoistic tendencies in mind. Therefore, just as the Taoists believed that everything was circular and interconnected in their society, so they proved it with their progress in medicine.

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# PSYCHOSOCIAL RECUPERATION FOLLOWING CARDIAC SURGERY

*By Dan Mendonca*

Cardiac surgery and angioplasty have advanced to the point where fatality rates for these procedures, performed electively in patients under 70 years of age, are less than 2% in many medical centers[1]. Unfortunately, there are patients who do not benefit to the extent that would be expected from successful surgery. For these patients, a poor social outcome is associated with lingering somatic complaints and a lack of confidence concerning physical exertion. These patients do not engage in activities of the type that their improved cardiac status might allow. Poor psychosocial adaptation is also linked with social isolation and low compliance with medical and exercise regimens [2].

It is well known that psychological distress figures prominently in a patient's rehabilitation following surgery for cardiac disease. Timberlake *et al* (1997) provide the following benchmarks regarding the pattern of depression after such surgery[3]: Eight days following surgery, 50 % are depressed due to discomfort, pain, and estrangement from the home setting. At eight weeks, 24 % and at twelve months, 22% are still depressed. Given, for example, that most coronary bypass patients at London Health Sciences Centre (LHSC) will be discharged post-operatively after five days or less, this means that many will have to cope with depressive symptoms at home. Depressive symptoms increase the probability of visits to the emergency department and frantic calls to health professionals on account of a cognitive state of helplessness and other symptoms involved in depression. Similarly, a sub-clinical level of pessimism involving negative self-perception has been found to be associated with a reluctance to return to work and a reduction in leisure activities[4].

Using a prospective sample of patients admitted for coronary angioplasty and coronary artery bypass, Levine *et al* (1996) found that both psychological depression and disease severity predicted the number of days of re-hospitalization when patients were followed for six months after discharge[5]. Statistical analysis revealed the independent contribution of psychosocial variables (in particular, in predicting frequency of patient symptoms) after indicators of left ventricular function (e.g. angina, dyspnea and fatigue) had been controlled for[5]. With this in mind, it should be possible to improve our ability to predict which patients will recover well and which will recover incompletely after heart surgery.

A recent study has found that patients with less severe disease pre-operatively may be more prone to depression following surgery[3]. It is possible that those patients who were most incapacitated prior to surgery received the greatest relief from their operation. Alternatively, patients who were under the impression that their disease severity was not very serious may have been ill-prepared for the subsequent incapacitation. Langosch *et al* (1992) reported that patients who perceived their operation as a purely technical event (avoiding emotional involvement) were more depressed post-operatively[6]. It is important, therefore, to take into account patients' expectations and their understanding of the extent of their disease.

During the early phase of recovery, there is heightened somatic concern and anxiety. Anxiety, in this case, results in activation of the sympathetic nervous system, a key modulator of cardiovascular function. Strategies aimed at inducing a relaxation response might be useful during this initial phase. Unfortunately, a high level of anxiety provides the motivation for relatively swift learning of maladaptive conduct. A perceived reduction in fear reinforces negative behaviours such as phobic responses, superstitious acts, and avoidance behaviour [7].

With reference to social disability, it has been found that 50 % of marriages may deteriorate after a myocardial infarction[8]. This might be due, in part, to changes in role imposed during the recovery process which often affect self-esteem. Patients and family could benefit from the opportunity to interact with well-adjusted former patients to develop positive expectations regarding the future.

Patients report experiencing specific problems of emotional adjustment following cardiac surgery. In a study involving focus groups of former patients, Border *et al* (1985) report the following[9]: i) going through a "downer" (e.g. crying for no reason, memory problems, crying because one cannot return home), ii) feeling fearful on leaving the security of the hospital, iii) fearing they will appear less attractive to their partners on account of their scar. Patients may go through different phases in terms of accepting emotional support. Some patients may prefer to "crawl into a hole" and wait while they either "die or get better". Others opt to have family milling about them, talking and doing all kinds of things.

Chest pain is perhaps the major symptom that concerns patients, spouses, and personnel. Patients should be encouraged to mentally review the experience of chest pain and its implications[6]. Medical staff can clarify misconceptions and provide new information to aid patients in appraising their physical condition. Patients can be taught to notice whether they change their rate of breathing, tense up specific muscles, change their posture, or focus on specific thoughts during the experience of chest pain. Techniques which can be used to counteract the anxiety associated with chest pain include breathing exercises, deep muscle relaxation techniques, imagery, and diversion (e.g. focusing on the idea that the pain will

quickly pass)[6].

One of the key ingredients of depression following surgery is "learned helplessness"—*ie*, a belief that the patient cannot meaningfully alter their own recovery. With respect to counteracting this effect, two major foci have been identified: symptom reporting and activity progression[6]. Both strategies are directed at helping patients regain a sense of personal control. In the first case, patients can be taught specific vocabulary which allows them to accurately describe bothersome symptoms (*eg*, chest pain). Positive reinforcement is given to patients when descriptors give clear information about the pain experience. Pain in the chest wall, for instance, can be readily differentiated from anginal pain. In the second instance, patients can be taught to assess the body's response to exercise and thus participate in planning activity progression. This might involve taking the pulse before and after specific activities. In this context, fatigue, shortness of breath and chest pain might be viewed as indicators of the body's slowly improving response to exercise (rather than imminent threats). The patient experiences a sense of control in helping to determine when their heart can successfully manage a particular load.

In addition to monitoring physical symptoms and activity progression, patients can be taught ways to better manage recurring worries regarding their future. These thoughts lead to changes in mood which can impact on a patient's ability to improve. The cognitive technique of "thought stopping" is one which can be used to arrest such ruminations[10]. Patients may also be disturbed by fluctuations in affect which are commonly experienced following heart attack. Counselors might be used to help patients articulate their troubling feelings and place them into perspective.

Interventions designed to promote patients' perception of control are one approach to improving psychosocial recovery following a cardiac event. Patients' perception of control (relating specifically to their cardiac disease) appears to be adaptable (amenable to change) and, indeed, predictive of later psychosocial recovery. In studies where patients were involved in planning aspects of their own rehabilitation programme, psychological distress was found to decrease as perceived control among patients increased[2].

Artinian *et al* (1995) sought to determine whether physical, psychological or social recovery differ for men and women during the first six weeks following coronary artery bypass[11]. Women in the study reported a significantly higher number of physical symptoms. This was especially true for activities involving ambulation. Women also had more symptoms of depression than men. (It is worth noting that female patients were more likely to be without a spouse.) Importantly, female patients experienced lengthier recoveries and were less likely to have adequate spousal support (e.g. with home management activities).

In recent years, controversy has arisen over the issue of long-term psychological maladjustment in patients following open-heart surgery. While Timberlake *et al* (1997) confirm an increase in the prevalence of depression following surgery, they report an eventual decrease in prevalence to a level below that seen prior to surgery 3. Perhaps patients' improved cardiovascular function following surgery can account for the long-term decline in depressive symptoms.

Beck *et al* (1995) report that the crucial component of depression may be the cognitive dimension[12]. Further investigation is needed to elucidate the course of depression and anxiety, particularly the cognitive core, following cardiac surgery. (The cognitive core refers to perceptions of diminished self-worth, helplessness and pessimism regarding the future). Providing interventional therapy for all patients receiving open-heart surgery would be both expensive and time-consuming. It may be possible, however, to identify those patients who may be at risk of showing poor postoperative psychological adjustment.

## SUMMARY

Although most patients experience a successful psychosocial recovery following cardiac surgery, a significant proportion experience persistent distress which impacts negatively on physical well-being and reintegration into ordinary work, leisure, and domestic activities. The potential economic benefit of assisting the psychosocial recuperation of such patients is substantial. Fundamental information regarding the mechanisms of emotional maladjustment could prove indispensable to the cardiac care team. This should continue to be an area of focus for cardiac rehabilitation research.

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# FEATURE ARTICLES

## A REVIEW OF NEW CARDIAC MARKERS

*By Norman Mah*

### INTRODUCTION

In the emergency room setting, early diagnosis is important in the initial treatment and management of patients presenting with acute onset of chest pain. Early monitoring in the coronary care unit and the use of thrombolytic therapy greatly decreases morbidity and mortality[1]. Diagnosis has traditionally been based on clinical history, physical examination, and electrocardiographic (ECG) findings. When World Health Organization (WHO) criteria (presentation of chest pain over 20 minutes, evolutionary changes on the ECG, and abnormal levels of cardiac enzymes)[2] are used to classify patients with suspected myocardial infarction, only 50% of all chest pain sufferers admitted to the CCU are confirmed as having this condition. Although the ECG can be performed easily and rapidly, specific changes may be absent or inconclusive in the early hours in about half of the patients arriving at hospital with acute myocardial infarction (AMI)[3]. Furthermore, approximately 2% of patients with AMI are inadvertently sent home[4]. It is for this reason that measurements of biochemical markers of myocardial muscle cell damage play an important role in the diagnosis of AMI.

In the past, tests for lactate dehydrogenase, aspartate transaminase, and creatine kinase were developed and widely used. These tests were later replaced by newer technology such as minicolumn and electrophoretic separation methods for measuring the serum CK-MB isoenzyme, a more cardiac-specific marker[5]. But these traditional cardiac markers (total CK and CK-MB activity) do not aid in the early diagnosis of AMI because they peak too late and are not specific for cardiac injury. In recent years, the search for more sensitive and specific markers of myocardial infarction has brought about a new generation of biochemical cardiac markers such as the mass concentration assay of CK-MB, CK isoforms of the isoenzyme CK-MB (MB2/MB1 ratio), myoglobin, and troponin I and T. In the following review article, these new biochemical markers will be examined.

### MYOGLOBIN

Myoglobin, an oxygen-binding cytosolic protein of low molecular weight, is normally found in cardiac and skeletal muscle. When necrosis of these muscles occurs, myoglobin is released into the serum and can be detected by radioimmunoassay as early as 1-4 h after cell death with a peak between 4-12 hours and a return to normal 18-24 h later[6,7,8]. Woo concluded that because myoglobin is an early and sensitive marker of necrosis, it is valuable for early detection and exclusion of AMI[9]. However, because myoglobin is also found in skeletal muscle, it has poor specificity, and can lead to many false positives in patients presenting with skeletal muscle trauma. Some researchers have suggested simultaneous measurements of a skeletal muscle specific marker, carbonic anhydrase III to resolve this limitation[10].

Myoglobin has been compared with CK-MB (activity and mass) in a number of studies with inconsistent findings. One study showed that the test for CK-MB mass was superior to that of myoglobin[11]. However, Brogan reported that myoglobin was a more sensitive marker of myocardial necrosis than CK-MB (mass) during the first 3h of presentation in the emergency department[12]. This was supported by Tucker, who showed that the sensitivity within 4 h of the onset of symptoms was 78% for myoglobin versus 63% for CK-MB mass[13]. Finally, another study showed no significant difference in the performance of myoglobin compared to CK-MB mass[15]. Bakker concluded that the best predictors of AMI within 4 h after onset of chest pain using WHO criteria were the combination of ECG and myoglobin[14].

Although myoglobin lacks specificity, its early release suggests that it may become an important diagnostic tool for triage of chest pain patients in the future[11,13,16]. This is supported by the fact that some hospital emergency departments have already instituted the routine use myoglobin to aid in triaging patients presenting with chest pain (*Ed. Note – LHSC-UC routinely measures myoglobin in the emergency department*).

### CREATINE KINASE

Creatine kinase is a cardiac enzyme that is released into the blood when myocardial necrosis occurs. It consists of three isoenzymes – CK-MM, CK-MB, and CK-BB, but it is the CK-MB isoenzyme which is most widely used as a biochemical marker for the diagnosis of AMI[16,17]. Specifically, serial measurements of CK and CK-MB are used to diagnose myocardial cell damage and its characteristic rise and fall in serial measurements is nearly pathognomic for AMI. The assay of CK-MB isoenzyme and the calculation of its percentage relative to total CK is the standard of reference for the diagnosis of AMI[18]. Although the sensitivity of CK-MB activity for AMI diagnosis is very high, cardiac specificity is compromised in patients with skeletal muscle trauma, myocarditis, chronic renal failure, cardiac surgery, as well as rare ectopic production in patients with tumors[19].

This problem has led to efforts to find more specific markers for AMI. In earlier studies, electrophoretic or chromatographic procedures were used to measure levels of CK-MB. This led the way for the production of CK-MB monoclonal antibodies, which were essential in the

development of rapid and cost-effective assay procedures using fully automated analyzers[5]. The development of automated mass assays for CK-MB also led to improvements in clinical sensitivity and specificity and turnaround time when compared to catalytical determinations done in the past[11,17]. However, CK-MB is not a perfect biochemical marker because 8-12 h may be required after the onset of symptoms for the test to be elevated above normal and yield a high sensitivity and specificity[19] (although CK-MB has been noted to rise earlier in some patients with large infarcts). Another major drawback is that CK-MB mass concentration has been shown to increase in the first 48-72 h with a return to normal within 72 h after the onset of chest pain in patients with known AMI. This leaves a relatively short diagnostic window of only 2-3 days[22,23].

## CK ISOFORMS OR SUBFORM

In addition to the three isoenzymes of CK, both CK-MM and CK-MB can be metabolized by enzymatic cleavage of the terminal lysine amino acid from the "M" subunit. High-voltage electrophoresis techniques can be used to separate and measure CK-MB and its two isoforms – CK-MB 2 and CK-MB 1 in an attempt to improve CK-MB sensitivity in the early stages of AMI. Bhayana found that time to positivity of both the mass monoclonal assay of CK-MB and the isoform assay were comparable, but noted greater difficulty in performing and interpreting the isoform assay[24]. Hetland and Dickstein reported that the isoform ratio was the most sensitive test in the early 0-3 h after the onset of chest pain and at admission to hospital[15]. In the following 3-5 h, no significant difference among the sensitivities of myoglobin, CK-MB isoform ratio and CK-MB mass concentration was found[15]. Puleo performed a study comparing CK-MB activity with CK-MB isoform in diagnosing AMI and has recommended widespread CK-MB isoform testing after finding reliable detection of AMI within the first 6 hours after the onset of symptoms[25]. However, no study comparing CK-MB mass with CK-MB isoform has been done at the present time.

There are some disadvantages to using CK-MB isoform testing. The time to perform isoform quantitation, difficulty of the procedure, lack of a practical 24-hour stat assay, difficulty in interpretation, as well as high costs will restrict the wide-spread implementation of this test until further developments are made.

## TROPONIN

The troponin complex plays an important regulatory role in the contraction of striated muscle. This complex consists of three protein subunits—troponin C, which binds to calcium and regulates contraction, troponin I, which inhibits actomyosin ATPase, and troponin T, which binds the troponin complex to the tropomyosin strand[22].

Troponin T and troponin I have amino acid sequences that differ in skeletal and cardiac muscle at various locations[22]. Antibodies have been developed which recognize these cardiac-specific sequences, and it is these antibodies which form the basis for cardiac troponin T (cTnT) and cardiac troponin I (cTnI) immunoassays[22]. Troponin C cannot be utilized as a cardiac-specific marker because its amino acid sequence is identical in both skeletal and cardiac muscle[22]. CTnT differs from cTnI in that the former is found in great amounts in the cytosolic pool and has a longer lifespan in the bloodstream. Cardiac troponin T also has a lower absolute cardiac specificity than cardiac troponin I[19].

Quantitative assays for both cTnT and cTnI tests have been shown to be more sensitive and specific than CK-MB for the diagnosis of AMI[19]. The enhanced specificity allows for more accurate diagnosis of cardiac injury, especially when skeletal muscle trauma is present. As well, troponin levels remain elevated up to 7-14 days after an AMI[18]. Thus, troponins can be measured long after myoglobin and CK-MB have returned to normal levels. This broader diagnostic window is advantageous in the minority of patients who delay seeking medical care because of equivocal symptoms or other reasons. However, the fact that troponins can detect cardiac damage days after infarction limits its ability to detect reinfarction.

A recent prospective study examined the use of a rapid, qualitative troponin T and troponin I test in patients arriving to the emergency department with acute chest pain. The results indicated that no patient was inappropriately discharged when the troponin T bedside test was routinely used[3]. Furthermore, when patients were tested 6 h after the onset of pain, 94% of patients with MI and without ST-segment elevation had a positive troponin T test, and 100% had a positive troponin I test[3]. Although the diagnostic specificity of these tests were somewhat low, these figures are nonetheless significant.

Cardiac troponin T has been recognized as a highly sensitive and specific assay for AMI in a number of studies[23,26]. Wu demonstrated in their study that cTnT was a sensitive marker of myocardial damage during the first 6 h, and was comparable with the "gold standard" CK-MB mass assay. After this time, the clinical sensitivity of cTnT surpassed that of CK-MB because of the prolonged release of cTnT into the blood[23]. The same study, however reported a diagnostic specificity for cTnT of only 46%, a lower specificity than in earlier papers. Another study found that cTnT to be more efficient than CK-MB in determining and excluding AMI[17]. Bakker found that the diagnostic sensitivity of troponin T was much better than that of myoglobin, CK, and CK-MB activity[14].

Cardiac troponin I, unlike CK-MB, is highly specific for myocardial tissue, and is not found in the blood of healthy individuals[19]. Troponin I has been shown to have great prognostic value. Antman examined the prognostic value of cardiac troponin I in patients with either unstable angina or non-Q-wave myocardial infarction. He found that cTnI is an independent risk factor identifying patients with unstable angina or non-Q wave MI who are at increased risk of death[27]. The prognostic value of cTnI was found to be greater in those patients presenting more than 6 h after the onset of chest pain[27]. Antman also reported that there was a direct relationship between the amount of cTnI and mortality. That is, the higher the level of cTnI, the greater the risk of mortality[27]. These findings are significant in that cTnI allows for the early identification of patients at increased risk of death.

A disadvantage for troponin use is that the assay for

troponins requires a dedicated instrument that is not widely available, as well as 90 minutes for completion. Furthermore, the cost of the reagents is much higher than those for CK-MB. A relatively new rapid troponin test assay, which allows the determination of troponin levels in whole blood at the patient's bedside shows some promise. It can be performed conveniently in the emergency room or in laboratories, and can potentially be used to aid in the triage of chest pain patients.

## CONCLUSIONS

Early diagnosis of myocardial infarction is of great importance in decreasing morbidity and mortality, especially with recent advances in thrombolytic therapy. Although the ECG remains the standard test for diagnosing AMI and initiating thrombolytic therapy, often it is unable to guide the clinician to definitive management. Therefore, alternative diagnostic methods must be used, especially in those patients without ECG changes or with unstable angina[3]. New biochemical markers have been shown to facilitate successful intervention by identifying individuals at risk of sudden death from an ischemic cardiac event. These markers are not only useful in aiding in the diagnosis of AMI, but they may also have valuable prognostic utility as well. Specifically, cardiac troponin I is an important prognostic marker of acute coronary syndromes or unstable angina. This allows some patients to be discharged home rather than being admitted to hospital resulting in enormous savings to the health care system.

Myoglobin, CK-MB, and troponin have all been shown to be valuable diagnostic tools for reliable and rapid detection of patients with AMI Early recognition of myocardial cell death will allow appropriate triage of patients with chest pain and the selection of therapeutic strategies.

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# HYPERTENSION IN PREGNANCY: AN UNUSUAL ETIOLOGY— A CASE REPORT

*By Andrea Lausman*

Hypertension presenting in, or being aggravated by pregnancy is a common occurrence. It is estimated that 6-10% of nulliparous women[1] will have a pregnancy complicated by hypertension. If a woman develops hypertension during her pregnancy, most clinicians initially assume the diagnosis of preclampsia or pregnancy induced hypertension. It is important to remember, however, that occasionally, the etiology of a condition characteristic or specific to pregnancy may be the result of some other pathology. A case is presented below in which the etiology of hypertension occurring in pregnancy was an aldosterone-secreting adrenal adenoma.

Primary hyperaldosteronism is a rare, but well-documented disease occurring during pregnancy. There have been less than twenty cases reported, the majority of which were due to an adrenal adenoma. Since surgery is the treatment of choice for active adrenal tumours, it is important to document the presence of a neoplasm so that it can be treated appropriately.

## CASE REPORT

A 33 year old nulliparous woman presented to the emergency department at $17^{+4}$ weeks gestation complaining of acute onset of proximal leg weakness. This came on quite suddenly after a three week history of migraine headaches, vomiting, and migratory myalgias involving her lower limbs bilaterally including her right hip, calf, left foot and calf. Significant past medical history includes a two year history of hypertension and headaches, for which she was taking atenolol.

On physical examination, abnormal findings included a blood pressure of 190/110, decreased power in the hip flexors and dorsiflexors at the ankles bilaterally, and pitting edema bilaterally to the knees. The only abnormal laboratory value was a serum potassium of 1.8 mmol/L (ref. 3.3 -3.5 mmol/L), and U waves present on the ECG. There was no proteinuria.

At this point, a tentative diagnosis of hyperaldosteronism was made, and the patient was admitted to hospital. Her potassium level was stabilized using potassium boluses and supplements. Investigations in hospital included a renal ultrasound and serum aldosterone levels. No adrenal masses were seen, but the aldosterone level was found to be elevated at 2041pmol/L. The blood pressure was stabilized using atenolol, and the patient was placed on potassium supplements.

At 29 weeks gestation the patient had an abdominal MRI which demonstrated a 2.5 cm adenoma on the left side. This confirmed the diagnosis of an adrenal tumour; it was concluded that the tumour was most likely secreting aldosterone.

As she continued with her prenatal care, her blood pressure was found to be high, but stable at 170/100. Her urine was normal until $33^{+6}$ weeks gestation when she had 1+ protein on the urine dipstick. A 24 hour urine collection for protein was done, and was found to be within the normal range at 400mg/day. Subsequent urine dips were normal, until her antenatal visit at $36^{+5}$ weeks, when she again had 1+ protein in her urine. Her blood pressure was becoming more volatile at this time as well. Since the patient was non-compliant and refused admission to hospital for fetal-maternal monitoring, she was induced at 37 weeks gestation. She had a normal labour and vaginal delivery which produced a healthy infant.

She has been subsequently referred to a surgeon for the removal of her tumour.

## DISCUSSION

Primary hyperaldosteronism, due most commonly to adrenal adenoma or bilateral adrenal hyperplasia, is the cause for approximately 1-2% of hypertension found in non-pregnant adults[2]. It is more common in women (2:1), and usually occurs between the ages of 30 and 50 years. However, there are less than twenty case reports of aldosterone secreting adrenal adenomas presenting during pregnancy.

The most common presentation, in pregnancy as well as non-pregnancy is symptoms of fatigue, muscle weakness, nocturia, lassitude and headaches. Blood pressure is mildly to severely elevated. In pregnancy, however, a complicating factor may be superimposed preclampsia; it may present quite a challenge to appropriately interpret all of the clinical findings.

The laboratory values which are abnormal include a low serum potassium, high serum aldosterone, low serum renin, and often a metabolic alkalosis. A definitive diagnosis can be made using CT scanning or MRI. Since CT scanning during pregnancy is not desirable, and MRI is an imaging modality which is becoming more accessible, these tumours may be identified using MRI. A renal ultrasound is often the first radiologic procedure done; however, as this case demonstrated, renal/adrenal ultrasound may not be helpful in making the diagnosis.

In a non-pregnant adult, the treatment of an aldosterone secreting adenoma is surgical resection[3]. However, medical treatment, in the form of spironolactone, an aldosterone antagonist, can be used to stabilize blood pressure and treat hypokalemia[4]. Other anti-hypertensives, such as calcium channel blockers and ACE inhibitors have been tried with some success[5].

Problems specific to the pregnant state arise in the treatment of hyperaldosteronism during pregnancy. Spironolactone is known to have antiandrogenic effects in humans; as well it can cause feminization of male rat

fetuses when administered to pregnant rats, it is therefore not recommended for use during pregnancy[6]. Since surgery is the definitive treatment, it is possible that if the disease was medically unmanageable, using anti-hypertensives and potassium supplements, then adrenalectomy could be performed during pregnancy[7].

In conclusion, hypertension during pregnancy is not an uncommon clinical finding. Although the vast majority of hypertensive, pregnant women will be diagnosed with preclampsia, it is important to remind oneself that the differential diagnosis of hypertension in pregnancy is quite diverse, and the case that one is dealing with may have a more unusual etiology that expected.

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# FACTOR V LEIDEN MUTATION AND VENOUS THROMBOEMBOLISM

*By Chantal Vaidyanath, BSc.*

Venous thrombosis is a multicausal disease in which genetic and acquired risk factors interact in an individual to determine whether or not a thrombotic event will occur at a specific point in time.[1] Recently, the Heart and Estrogen Replacement Study (HERS), the first major placebo-controlled clinical trial of hormone replacement therapy (HRT) in the secondary prevention of coronary heart disease was published. Over an average of 4.1 years of follow-up, HRT failed to reduce the overall rate of coronary heart disease events, but increased thromboembolic events (a secondary outcome measure) by 2.89 times.[2] In the past five years, advances in the genetics of thrombosis have resulted in the elucidation of novel coagulation abnormalities that predispose to venous thrombosis. In particular, a defect in the hemostatic pathway, called activated protein C (APC) resistance, and its underlying mutation, factor V Leiden, were found to be common in the population (3% to 7%).[3,10,14,15,16]

They are associated with substantially higher risks of venous thromboembolism among patients with a co-existent predisposition for thrombosis, such as advanced age, use of oral contraceptives, hyperhomocysteinemia, and deficiencies of protein C and protein S.[3] To date, the thromboembolic risk in postmenopausal women with the factor V Leiden mutation has not been studied. The intent of this review is to establish a rationale for research into the possible association of venous thromboembolism in postmenopausal estrogen users and the APC resistance phenotype, or the factor V Leiden mutation.

### Risk Factors for Venous Thrombosis

Risk factors for venous thrombosis are different from those for arterial thrombosis, and are classified into genetic and acquired risk factors. Many acquired risk factors for venous thrombosis have been identified, such as pregnancy, the puerperium, immobilization, surgery, trauma, lupus anticoagulant, malignant disease, and female hormones.[1] For example, oral contraceptive use is associated with a four-fold risk for venous thrombosis above baseline.[6] The risks of venous thromboembolism with hormone replacement therapy are also well-established. Prior to the HERS trial, researchers in Britain and in the United States found relative risk estimates for venous thromboembolism in current users of hormone replacement therapy of 3.5 and 3.6, respectively, compared with non-users or past-users.[4,5]

**ABOUT THE AUTHOR**

*Chantal Vaidyanath is a third-year medical student at the University of Western Ontario. Before entering medical school, she completed a BSc. in Biochemistry at the University of Ottawa.*

The genetic risk factors for venous thrombosis include disorders of the clotting system, such as protein C and protein S deficiencies, antithrombin III deficiency, prothrombin 20210A, hyperhomocysteinemia and resistance to activated protein C.[1] Resistance to APC was first described in 1993 by Dahlback *et al*, and it has been subsequently shown that in the majority of cases, it is caused by what is now known as the factor V Leiden mutation.[7,8]

### Activated Protein C Resistance and the Factor V Leiden Mutation

In the protein C/protein S pathway of coagulation inhibition, protein C is activated (ie becomes an active protease) when it binds to thrombomodulin, an endothelial membrane protein.[9] On a phospholipid surface, activated protein C, in the presence its cofactor, protein S, and calcium ions, inhibits coagulation by proteolytic cleavage of activated factors V and VIII, thus mainly acting on the feed-back activation of the intrinsic pathway of coagulation.[10,11] (Fig. I). The factor V Leiden mutation involves a single adenine-for-guanine point mutation in the gene encoding for coagulation factor V which leads to the replacement of arginine by glutamine at position 506. This position is one of the three cleavage sites on factor V for APC, and thus the mutation causes the activated form of factor V (Va) to be degraded at a slower rate than normal factor Va.[3] This results in the APC resistance phenotype, which causes increased thrombin formation and a lifelong hypercoagulable state.[12] The factor V Leiden mutation is inherited in an autosomal dominant fashion.[10] In 1997, the presence of a factor V genetic component other than factor, the HR2 haplotype, was described in patients who did not have the $V_{R506Q}$ mutation. This genetic component, is also able to contribute to the APC resistance phenotype in patients with venous thromboembolism.[13] The original factor $V_{R506Q}$ mutation will be the focus of this review, however, because it has been studied extensively, and henceforth, use of the term "factor V Leiden mutation" will refer to the $V_{R506Q}$ mutation.

Unlike other inherited defects of hemostasis, such as protein C and S deficiencies, and antithrombin III deficiency, factor V Leiden mutation is common. The carrier frequency of factor V Leiden mutation in healthy control populations ranges from 3% to 7% in Europe and the United States and may be as high as 15% in some selected groups.[10,14,15,16] It is most prevalent in white persons (5.27%) and is notably uncommon in Asian and African populations, a fact that may explain the decreased risk for venous thromboembolism in these groups.[17,18]

### Factor V Leiden Mutation and Risk of Venous Thromboembolism

In referral populations of patients with venous

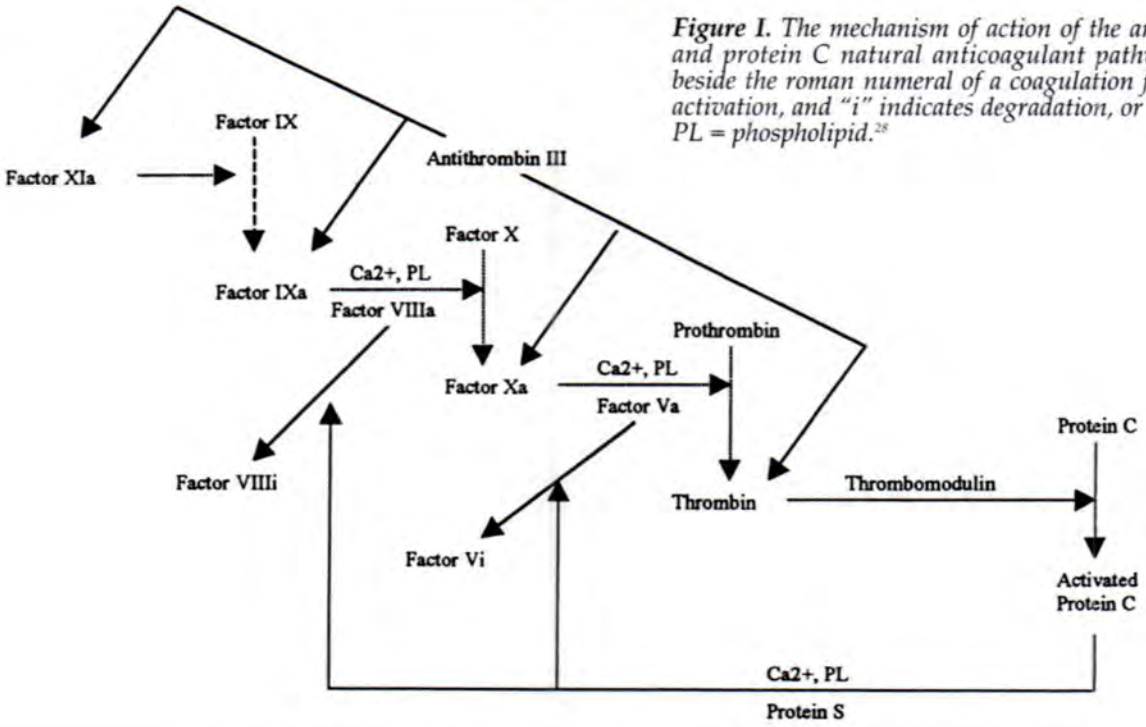


***Figure 1.*** *The mechanism of action of the antithrombin III and protein C natural anticoagulant pathways. The "a" beside the roman numeral of a coagulation factor indicates activation, and "i" indicates degradation, or inactivation. PL = phospholipid.*[28]

thromboembolism, factor V Leiden mutation is the most common identifiable risk factor, with a prevalence of 11% to 37%.[10,14,19,20,21] Heterozygous carriers of factor V Leiden have a seven-fold increased relative risk for venous thromboembolism versus non-carriers. Homozygous individuals have an alarming 80-fold increased relative risk of thrombosis. Still, most homozygous patients do not develop thrombosis until adulthood and may remain symptom-free until old age.[21] This is likely because venous thrombosis a result of the interaction between concomitant risk factors in a given individual.[1] Homozygous individuals also experience their thrombosis at a much younger age than heterozygous individuals (31 vs. 44 years) and non-carriers (46 years).[8]

Interestingly, studies have found that the majority of patients with venous thromboembolism who were identified as homozygous for the factor V Leiden mutation were women, and it was felt that these patients had become symptomatic due to their use of oral contraceptives.[21,22] An earlier population-based case-control study had in fact shown that women who carried the factor V Leiden mutation and who used oral contraceptives had a more than 30-fold increase risk of thrombosis compared to women who did not hav either risk factor.[6] Clinical studies also indicate that factor V Leiden mutation is associated with increased risks for venous thrombosis during pregnancy.[23,24,25] Thus, there is ample evidence of an interaction between genetic and acquired risk factors for venous thrombosis, where in combination they can produce an effect that exceeds the sum of their separate effects.

**Future Directions**

This year, the first report of an acquired activated protein C resistance in the postmenopausal period, was published by Marcucci et al.[12] This APC resistance was not associated with the factor V Leiden mutation, but with high plasma levels of factor VIII, which the authors propose would require more APC for a comparable anticoagulant effect. The authors admit, however, that the factor V genetic component marked by the HR2 haplotype may be responsible. Nevertheless, this finding in postmenopausal women raises the question of risk of venous thromboembolism in users of hormone replacement therapy who have APC resistance or who are carriers of either factor V genetic mutation. Given that the risk of venous thrombosis increases with age,[26] and that HRT in itself increases thromboembolic risks, it is possible that postmenopausal women with the factor V Leiden mutation who are taking hormone replacement therapy could be at a very high risk for venous thromboembolism. These are questions which need to be addressed if physicians are to be informed about the risks of prescribing hormone replacement therapy. At a simpler level,even the effect of menopause on the incidence of venous thrombosis is yet to be determined.

The study of APC resistance could become relevant in explaining the increased risk for venous thrombosis associated with postmenopausal estrogens. Should we screen for the presence of APC resistance in women requesting HRT? This question has been debated in the literature concerning oral contraceptive use. Let us consider the example of screening for factor V Leiden in

women requesting oral contraception, assuming that all fatal thromboembolic events are attributable to the factor V Leiden mutation. Vandenbroucke et al estimated that almost half a million women would require screening to identify the 20,000 to 25,000 women who carry the mutation and would be denied oral contraception, in order to avoid one death per year.[27] The costs of such a program would be formidable.

For now, physicians must be aware that a careful emphasis on thromboembolic events in both the personal and family histories of patients can often identify those who might need to avoid oral contraception and hormone replacement therapy, or who should be anticoagulated if they choose such treatments. But perhaps in patients identified as being high risk, it is justified to investigate the coagulation status. This would identify patients for whom hormone replacement therapy need not be withheld, and would differentiate them from patients who should only take hormone replacement therapy if they take concomitant anticoagulant therapy. Thus screening for APC resistance, particularly in high risk populations, should be considered.

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# HEART DISEASE IN WOMEN: RESOLVING MISCONCEPTIONS

*By Matthew A. Crystal*

In the past decade there has been a strong drive to discover the sex differences regarding heart disease.[1] Many misconceptions have been corrected in the literature; however, men, women and their physicians alike are still not keeping abreast of new discoveries. From a physician's standpoint, educating one's patients can be one of the most effective means of preventive medicine. Unfortunately, misconceptions still prevail, allowing symptom recognition and lifestyle changes to become less effective as time passes.

What are these misconceptions and what are the facts? Heart disease is now the number one killer of both men and women in the United States and Canada.[1,2,3] It had been believed for a long time that heart disease only affects older women who are post-menopausal. While it is true that the effects of estrogen have a cardio-protective function, this only delays the onset of disease. Studies have shown that a woman's first presentation to the health care system is between three and ten years later than men on average, but the outcomes for women are worse after having a myocardial infarction.[4] These patterns reinforce the notion that women should be better educated about their risks of heart disease.

Lifestyle improvements and risk factor modifications have been implemented aggressively with men, in order to reduce their prevalence of heart disease. This same aggressive preventive medicine should be used in affecting the outcomes that women face. Although 41% of all deaths in women are related to heart disease, women continue to believe that their major health risk is breast cancer. In the 1990 Ontario Health Survey, 81% of women stated their most serious health concern to be breast cancer,[5] when in reality the number of women who die from heart disease each year is almost as great as the number of deaths in women from all cancers combined.[2] These misconceptions not only give women false impressions about their general health, but their ability to modify their risk factors is severely hindered as well.

As a member of the health care system, the physician's role is to diagnose, treat and educate patients. Education is an incredibly important factor in successfully implementing preventive medicine protocols. When people are empowered with knowledge they are more likely to respond to risk factor modifications. Where do most women receive pertinent health information? Their physicians. Herein lies another problem. A 1997 study in the Journal of Women's Health reports that 59% of the subjects who responded believed that their primary care physician had inadequately counseled them about heart disease. Many women also felt that they were never properly assessed for heart disease risk factors.[2]

These biases have been propagated, historically, by the exclusion and under-representation of women in cardiovascular clinical trials.[6] As national regulations have changed in the past decade, study populations have become more representative of the patient populations that are seen each day. These changes have led to many large scale research projects that will report their findings on women's health in the early part of the 21st century.[7] The goal of such projects is to correctly assess the health risks of women, while correctly documenting the signs and symptoms with which they will present.

What is known already? Gender differences have been described in clinical presentations and in risk factor profiles. For example, research has shown that women suffer from heart disease, with an average age of onset ten years greater than that of men. Women are more likely, however, to face a worse prognosis after a myocardial infarction than men, and their prognosis following surgical therapy for coronary artery disease is also worse than that for men. In terms of clinical presentation, chest pain in women is not as specific an indicator for heart disease as is the case with men. This does not allow one to dismiss the possibility of heart disease. On the contrary, a very careful history should be elicited to ensure that the number one killer of women is not overlooked, especially because 50% of women with heart disease first present with angina.

Men and women do share a lot of symptoms and risk factors, but in different ways and with a different emphasis. Smoking is a strong predictor of heart disease in both men and women, to the point that women who smoke lose their protective estrogen advantage and are just as likely to develop heart disease men of the same age.[1] Diabetes is a prominent risk factor for men and has been shown to be more so in women. In terms of cholesterol status, hypertriglyceridemia and low levels of HDL are more predictive than total cholesterol status and elevated LDL levels; the opposite is true for men. Another modifiable risk factor which has been ignored to a large extent in women is sedentary lifestyle. Men tend to lead more active lives than women, with an astounding 83% of women in a self-reporting database being rated as inactive. These differences do exist, but many of the strategies for modifying risks are not different.

Research protocols have come a long way in the last ten years to actively report on women's health issues. With respect to heart disease, women have been shown to have similar risks to men that should not only be recognized, but monitored and treated with special

**ABOUT THE AUTHOR**

*Matthew A. Crystal is in his third year of medical school at UWO. He previously completed three years of undergraduate science at York University.*

emphasis on the gender differences that do exist. Women have different needs than men, but the important thing to remember is that every patient who visits a doctor has their own special story, needs and risk factors. The most important tool that we have still remains a good, detailed history. Never underestimate its usefulness.

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# GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS: NOVEL ANTIPLATELET AGENTS IN CARDIOVASCULAR MEDICINE

*By Tisha Joy, Meds 2001*

Coronary artery disease (CAD) is one of the leading causes of death in developed countries. The atherosclerotic plaques in CAD consist of two main components: a fibrous cap and a lipid core. Disruption of the fibrous cap leads to exposure of the underlying components such as lipid, foam cells, and tissue factor, resulting in platelet aggregation and ultimately, thrombus formation. This process of atherosclerotic plaque disruption leading to platelet aggregation and formation of associated thrombus defines the acute coronary syndrome (ACS), a continuum of clinical manifestations ranging from unstable angina to non Q-wave myocardial infarction or Q-wave myocardial infarction.[1] Platelets are, thus, key players in the triggering of the acute manifestations of CAD.

Antiplatelet therapy, such as aspirin, has become mainstay in both the primary and secondary prevention of cardiovascular events. However, aspirin is a relatively weak antiplatelet agent since it is only able to prevent thromboxane A2-dependent platelet aggregation without any inhibition of thromboxane A2-independent aggregation. Circulating mediators for thromboxane A2-independent platelet aggregation include adenosine diphosphate (ADP), thrombin, serotonin, and shear rate.[2] In fact, more than a hundred different mechanisms can result in platelet activation. Yet, regardless of the pathway chosen, all mechanisms lead eventually to a final common pathway involving the platelet surface glycoprotein IIb/IIIa receptor.

The glycoprotein IIb/IIIa receptor, a member of the integrin family, is the most abundant receptor on the platelet surface. For platelet aggregation to occur, a conformational change in the glycoprotein IIb/IIIa receptor from the inactive to the active state must occur before the receptor will bind to its primary ligand, fibrinogen. Fibrinogen causes platelet crosslinking necessary for aggregation by simultaneously binding to the glycoprotein IIb/IIIa receptors of two adjacent platelets.[3] Thus, since glycoprotein IIb/IIIa receptors comprise the final common pathway leading to platelet aggregation, blocking these receptors via antagonists would be an effective means of preventing platelet aggregation, thrombus formation, and ultimately, cardiovascular ischemic events.

**Abciximab** is one such glycoprotein IIb/IIIa receptor antagonist that is currently being investigated for clinical use. It is a chimeric monoclonal antibody Fab fragment (c7E3) that binds with high avidity to the glycoprotein IIb/IIIa receptor as well as to the "v$3 vitronectin receptor, which is involved in smooth muscle cell migration and proliferation.[4] The first large-scale double blind randomized control trial to investigate the potential benefits of using abciximab to prevent cardiovascular events was EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications). This trial involved 2099 patients undergoing high-risk atheroplasty or atherectomy. All patients received aspirin as well as heparin. The patients were then randomly assigned to one of three treatment arms: 1). abciximab bolus + abciximab infusion; 2). abciximab bolus + placebo infusion; or 3). placebo bolus + placebo infusion. The treatment arm of abciximab bolus + abciximab infusion demonstrated a significant 35% reduction in the composite primary end point of death, nonfatal myocardial infarction, refractory ischemia, or urgent revascularization within 30 days, when compared to the placebo group. Only a 10% reduction was noted in the abciximab bolus group compared to placebo. There was, however, a two-fold increase in the risk of bleeding complications and need for transfusions in the abciximab bolus + abciximab infusion group compared to control. Yet, the reduction in ischemic events noted in the abciximab bolus + abciximab infusion treatment arm persisted at both 6 months and 3 years followup.[5-7]

The EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockage) trial was conducted next to determine whether low-risk patients could also benefit from abciximab. The trial was prematurely terminated since the abciximab treatment group had a 57% reduction in the composite 30 day endpoint of death, myocardial infarction, or urgent revascularization as compared to control (standard heparin therapy). Interestingly, unlike the EPIC trial, there was no increased risk of bleeding in the abciximab treatment group. It was determined that the higher bleeding rates in the EPIC trial were due to the use of high dose adjuvant heparin therapy. Thus, the EPILOG trial demonstrated two critical points: 1). The benefits of reductions in ischemic complications from abciximab treatment could be extended to low-risk patients; and 2). The risk of bleeding complications could be decreased by using only low doses of adjuvant heparin therapy.[8]

**ABOUT THE AUTHOR**

*Tisha Joy is a third-year medical student at the University of Western Ontario. Prior to entering medical school, she completed a Bachelor of Science (Honours) degree in the Microbiology Specialist program at the University of Toronto.*

The ability of platelet glycoprotein IIb/IIIa receptor antagonists to not only prevent progression to myocardial infarction in patients with unstable angina but also avoid myocardial infarction at the time of coronary intervention was first demonstrated in the CAPTURE (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Therapy) trial. Patients were randomly assigned to receive either abciximab or placebo infusion prior to angioplasty and continuing until 1 hour after the procedure. The trial was terminated prematurely since there was not only a 29% decrease in the composite 30 day endpoint of death, myocardial infarction, or revascularization but also a substantial 71% reduction in the progression to myocardial infarction prior to percutaneous transluminal coronary angioplasty (PTCA). The results of this trial, thus, showed that abiciximab could also provide benefits for patients with unstable angina not undergoing angioplasty.[9]

Based on the results of the above trials, it seems reasonable to consider the possible application of abciximab to the management of acute myocardial infarction. Animal studies have demonstrated increased thrombolytic activity as well as prevention of early reocclusion after reperfusion with the administration of glycoprotein IIb/IIIa receptor antagonists.[10,11] Pilot studies with humans have indeed reported improved patency rates of infarct-related artery via increased speed of reperfusion, although only a small number of patients were involved.[12] Based on these encouraging results, the potential for using glycoprotein IIb/IIIa receptor antagonists in the management of acute myocardial infarction does certainly exist.

Abciximab is just one of the many glycoprotein IIb/IIIa receptor antagonists being currently studied. The synthetic agents under investigation include lamifiban, eptifibatide (Integrilin), and tirofiban which, unlike abciximab, are all specific for the glycoprotein IIb/IIIa receptor alone. All four agents can only be used parenterally.[4] Oral glycoprotein IIb/IIIa receptor antagonists also exist, including sibrafiban, xemilofiban, and lefradafiban. Trials with oral agents are currently underway to determine efficacy and safety. Thus far, studies have reported consistent blockade of receptors ranging from 50-80% depending on the agent. However, these studies have noted an increase in mucocutaneous bleeding with the oral agents.[13-15] Yet, the importance of the oral agents lies in their potential use in both acute situations as well as in secondary prevention. Table 1 lists some of the possible indications for the oral glycoprotein IIb/IIIa receptor antagonists.

Since the glycoprotein IIb/IIIa receptor antagonists act at the final common pathway required for platelet aggregation, these antagonists offer several important advantages: 1) their effect on platelet aggregation will be considerably more potent than any of the other available antiplatelet agents; 2) their efficacy can not be bypassed by redundant pathways of platelet activation; and 3) the onset of action of parenteral agents is nearly instantaneous.[16] These advantages together with the clinical trials supporting the use of glycoprotein IIb/IIIa receptor antagonists to reduce ischemic complications explain the huge interest currently in these antagonists as a novel means for combatting the acute manifestations of cardiovascular disease, and in particular, as a possible addition to the current therapy for the acute coronary syndromes, including Q-wave myocardial infarction, non Q-wave myocardial infarction, and unstable angina.

**Table 1 Potential Indications of Oral Inhibitors of Platelet GPIIb/IIIa Membrane Receptor[2]**

| |
|---|
| *Acute Indications* |
| Percutaneous coronary interventions |
| Acute coronary syndromes |
| Unstable angina |
| Non Q-wave MI |
| MI with ST elevation |
| *Secondary Prevention* |
| Percutaneous coronary interventions |
| Acute coronary syndromes |
| Stroke |
| *Prevention of acute events in patients with stable disease* |
| *Primary prevention in high-risk individuals* |
| *Control of atherothrombosis and progression of coronary artery disease* |

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# THE RATIONALE AND EVIDENCE FOR THE USE OF BETA BLOCKERS IN THE MANAGEMENT OF CHRONIC HEART FAILURE

*By Munir Boodhwani*

## Introduction

Heart Failure is a major cause of morbidity and mortality in North America. The incidence of heart failure in the general population varies from 1 to 5 per 1000 per annum and can be as high as 40 per 1000 per annum for people over the age of 75 years. The prevalence ranges from 3 to 20 per 1000 for the general population and can be as high as 130 per 1000 in people over the age of 65 years.[1] Despite the heavy burden of disease, there is no universally agreed upon definition of heart failure. The diagnosis is made clinically and therefore, there is no one 'gold standard' test to confirm the diagnosis.[1] The primary signs and symptoms include shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, fatigue, peripheral edema and elevated jugular venous pressure. This article will briefly discuss the medical management of chronic heart failure focusing on the role of beta blockers.

## Medical Management of CHF

The medical management of chronic heart failure (CHF) is a complex undertaking and typically involves the use of multiple classes of drugs. The goals of treatment are to reduce symptoms, decrease the number of recurrent hospitalizations, and to improve survival.[2]

Diuretics are often the first line treatment for acute exacerbations of heart failure. They work by reducing excessive salt and water retention and therefore, decrease the preload which, in turn, results in a decrease in symptoms from pulmonary and systemic congestion. Although the impact of long-term diuretic use on survival is difficult to evaluate, their ability to reduce symptoms has made them one of the mainstays of heart failure treatment.[2] Angiotensin Converting Enzyme (ACE) inhibitors have made a significant impact on heart failure treatment and numerous Randomized Controlled Trials (RCTs) have been conducted to evaluate their impact on survival. It has been found that ACE inhibitors reduce mortality by about 23% when compared to placebo. This effect was shown to be consistent across all New York Heart Association (NYHA) classes and all ACE inhibitors.[4] Digoxin, a cardiac glycoside which is commonly prescribed in heart failure, has been shown to have no impact on mortality but does decrease the risk of hospitalization by approximately 30%.[5] Additional drugs used to treat heart failure include organic nitrates, calcium channel blockers (e.g. Amlodipine), antiarrhythmics (e.g. Amiodarone), Angiotensin II receptor blockers (e.g. Losartan), Spironolactone as well as Beta Blockers which will be discussed below.

**ABOUT THE AUTHOR**

*Munir Boodhwani is currently a third-year medical student at UWO. He previously received a BSc in human biology from the University of Toronto. He has a strong interest in cardiovascular medicine.*

## Rationale for Beta Blocker Use

The sympathetic nervous system has long been known to play a significant role in the pathophysiology of heart failure. When ventricular dysfunction leads to a decrease in cardiac output, there is a baroreceptor-mediated increase in sympathetic tone, which has several consequences. In the short term, it results in increased myocardial contractility, tachycardia, arterial vasoconstriction with a consequent increase in afterload, and venoconstriction with a consequent increase in preload. Long-term activation of these compensatory mechanisms results in remodeling and hypertrophy of the myocardium and also leads to myocyte toxicity, apoptosis, and altered gene expression.[7] Norepinephrine is known to be directly toxic to myocardial cells, an effect mediated through calcium overload and induction of apoptosis.[6] Since the failing heart is dependent on this constant sympathetic drive, beta blockade was thought to be contraindicated in patients with heart failure.[6,7] However, if beta blockers can be tolerated in the short-term, then they have been shown to have beneficial effects on ventricular function likely due to reduced myocardial toxicity. An up-regulation of β-receptor expression, which occurs in response to treatment with a beta blocker, is also associated with improved ventricular function.[7]

## Important Properties of Beta Blockers[8]

Beta Blockers have certain important characteristics which can affect their efficacy and usefulness. They are briefly described below:

- *Cardioselective vs. nonselective*—β1 receptors are responsible for most of the cardiac effects of beta blockers whereas β2 receptors are prevalent in pulmonary tissue. Therefore, cardioselectivity of beta blockers is simply a measure of the ability of the drug to more potently antagonize the β1 receptor as opposed to the β2 receptor. This is also thought to be the reason why cardioselective beta blockers are better tolerated in asthmatic patients. Bucindolol, propranolol, and carvedilol are examples of nonselective beta blockers whereas bisoprolol and metoprolol are examples of cardioselective ones.

- *Lipophilicity vs. hydrophilicity*—The lipophilicity of a beta blocker allows it to penetrate the central nervous system and therefore, potentially alter the vagal tone which is already altered in heart failure.
- *Inverse Agonism*—This is a property by which an antagonist may inactivate an unoccupied active state receptor. An agent with a high degree of inverse agonism may have a greater degree of negative inotropic and chronotropic effect.
- *ISA/Partial Agonism*—A beta blocker with this property partially stimulates the receptor while blocking the effects of the sympathetic nervous system on the receptor.
- *Ancillary properties*—Carvedilol has a very prominent non-hemodynamic property i.e. antioxidant effects which may play a role in heart failure possibly by reducing apoptosis in myocardial tissue.[9]

**Evidence for Beta Blocker Use**

Although numerous RCTs have been conducted on heart failure patients to evaluate the effects of beta blockers on hemodynamics, exercise, and quality of life, relatively few RCTs have measured the impact of beta blockers on morbidity and mortality. The results of three of the major trials, which involved a large number of patients and used mortality as their primary endpoint, are discussed below.

In May 1996, The U.S. Carvedilol Heart Failure Study Group published the results of a trial that involved 1094 patients and compared the effects of Carvedilol to placebo. This trial was discontinued early due to the obvious survival benefit in the Carvedilol group. The conclusions were that the relative risk reduction (RRR) in mortality due to Carvedilol was 65% and there was also a relative risk reduction of hospitalization due to cardiovascular causes of 27%.[10]

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), published in January 1999, studied the effect of bisoprolol (a cardioselective beta blocker) on patients with NYHA class III or class IV heart failure. This trial was also stopped early and demonstrated a reduction in risk of mortality of 32% as well as a significant decrease in the number of sudden deaths (RRR – 44%) in patients on bisoprolol vs. placebo. Although, the effect was consistent across both NYHA classes, the greatest effect was seen in patients with NYHA class III heart failure at baseline.[11]

The third major trial is the most recent and was published in June 1999. Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) studied 3991 patients with NYHA class II – IV heart failure and was also stopped early due to a 34% reduction in all-cause mortality. It also demonstrated a significant decrease in sudden deaths (RRR - 41%) as well as deaths from worsening heart failure (RRR - 49%), which was consistent across all NYHA classes.[12]

In addition, a meta-analysis of double-blinded, placebo-controlled, randomized trials published in May 1998 combined the results of 18 trials with a total of 3023 patients. The authors concluded that beta-blockade increased ejection fraction by an average of 29% and reduced the risk of all-cause mortality by 32%. Another important finding was that there was no difference in mortality risk reduction between cardioselective and nonselective agents.[13]

**Some Considerations**

It is important to note a few characteristics pertaining to the above trials, which help determine the criteria for beta blocker use.

- In all three major trials above, beta blockers were added to standard optimal therapy, which included ACE inhibitors and diuretics.[10-12] In the Carvedilol trial, the patients were also on digoxin.[10]
- All patients included in these trials were stable in terms of heart failure symptoms, regardless of the NYHA class that they belonged to.[10-12]
- The mean age of the patients included in these trials was between 58 and 63 with very few patients over the age of 75 years.[10-12] A significant portion of patients in the general population presenting with symptoms of heart failure are over the age of 75 years.
- Since ventricular fibrillation has been documented as the major cause of sudden death in heart failure patients, the significant decrease in sudden deaths in the beta-blocker group suggests a possible antiarrhythmic effect of the drug.[12]

**Conclusion**

Beta blockers have been known for many years to have beneficial effects in patients with coronary artery disease. Their role in the treatment of heart failure, however, has been unclear and they have traditionally been avoided for fear of exacerbation of the disease process. Recent studies have clearly demonstrated a survival benefit of long-term beta blocker use in addition to treatment with ACE inhibitors and diuretics in patients with stable symptoms of congestive heart failure. Thus, beta blockers should be given to all patients with mild to moderate heart failure in the absence of any contraindications (severe asthma, etc). The role of beta blockers in treating NYHA class IV is still unclear, and caution should be exercised when treating elderly patients (age > 75) due to lack of clear evidence. Ongoing trials are currently underway to determine the effects in these high risk groups as well as in patients with asymptomatic left ventricular dysfunction.

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Ω

# PULSUS ALTERNANS: MECHANISM AND CLINICAL SIGNIFICANCE

By Peter Kim

## Definition and History

Pulsus alternans (mechanical alternans) is the phenomenon of alternating strong and weak beats in the presence of regular intervals. It is not synonymous with electrical alternans which indicates a beat to beat alternation in one or more components of the electrocardiogram. Pulsus alternans was first described under experimental conditions in a frog's heart over a century ago by Gaskell.[1] The clinical description of pulsus alternans by Traube was made even earlier in 1872.[2] Since then, alternans has been studied both in humans and experimental animals and there has been continuous debate about its underlying mechanism and clinical significance.

## Proposed Mechanisms

The classic debate about the mechanism which precipitates pulsus alternans is staged between the hemodynamic argument and the contractility argument. The former employs the concept of alternating ventricular filling and the latter, an intrinsic defect in the myocardium as a possible factor contributing to the alternating beats. Recently, a cellular mechanism hypothesis has emerged.

### *The Hemodynamic Argument*

This argument is based on the Frank-Starling mechanism that involves the alternation of ventricular filling (preload).[3] A ventricular premature contraction (VPC) is one of the events that has been observed to result in pulsus alternans. It has been proposed that although the VPC would have a relatively low ventricular filling, the beat following it would have an enhanced stroke volume and its systole would last longer. On the next beat, the diastole would be shorter and as a consequence, the resulting lower ventricular end diastolic volume would result in lower stroke volume and aortic pressure. This sequence would continue, manifesting as alternating strong and weak pulses. This hypothesis was first suggested by Wenckebach[4] in 1902. Although there have been some studies in animals and humans that support this hypothesis,[5] recent studies against the hypothesis have suggested that the hemodynamic abnormality is not the primary mechanism underlying pulsus alternans.[6]

### *The Contractility Argument*

This argument is based on the hypothesis of an intrinsic myocardial defect that inevitably results in an aberrant contractility of the heart. Although it is still not clear what the basic mechanism of the contractile disturbance due to the myocardial defect is, a few studies on pressure-volume relationship in an intact heart demonstrated alternation of contractility as the primary mechanism underlying alternans.[7,8] In a study on isolated canine heart preparations, the slope of the end-systolic pressure-volume relationship was significantly greater than those of weak beats, suggesting that alternating contractile state is the source of alternans.[9] Alternation of ventricular filling was observed in these studies, but it was secondary to the changes in contractility.

### *The Cellular Argument*

Alternation of the action potential duration and alternation in intracellular $Ca^{2+}$ cycling to and from the sarcoplasmic reticulum have been the basis of this argument. It was been suggested that alternation of action potential duration would result in mechanical alternans by altering sarcoplasmic reticular $Ca^{2+}$ release. There are several lines of evidence against this theory[10] and mechanical alternans has been associated with both prolonged and shortened action potentials.[5] Although action potential duration does not seem to play a major role in mechanical alternans, there is mounting evidence for the role of calcium in alternans. Recent studies have shown the phenomenon of "calcium alternans" (alternating large and small calcium currents in regular intervals) associated with mechanical alternans in isolated animal ventricular muscle.[10,11] This observation supports the role of $Ca^{2+}$ as the principal factor in mechanical alternans, and the favored view at present is that mechanical alternans represents a $Ca^{2+}$ cycling phenomenon involving the sarcoplasmic reticulum.

## Clinical Relevance of Pulsus Alternans

### *Physical Examination*

Pulsus alternans is more readily recognized by sphygmomanometry than by palpation. As the blood pressure cuff is slowly deflated, only alternate beats are heard for a number of millimetres of mercury below the systolic level and then all beats are heard. When the systolic pressure alternates by more than 20 mm Hg, it can be detected by palpation of peripheral pulses (especially the femoral) rather than the central pulse.[12] To avoid the superimposition of respiratory variation of the pulse, palpation should be carried out while the patient holds his/her breath in mid-expiration. Total alternans occurs when the left ventricular systolic pressure is less than the aortic pressure so that the aortic valve fails to open, resulting in apparent halving of the pulse rate. Decrease in venous return by maneuvers such as tilting the patient in upright position and nitroglycerin administration may exaggerate pulsus alternans and assist in its detection.[12]

In the course of its detection, pulsus alternans should be differentiated from conditions with similar examination characteristics. Pulsus bigeminus occurs when the cardiac rhythm is bigeminal with the premature beats decreasing stroke volume and systolic peak pressure. Pulsus

paradoxus is a decrease in pulse amplitude of greater than 10 mm Hg during inspiration and is classically seen in pericardial tamponade, possibly in constrictive pericarditis (although less commonly), and in obstructive airway disease[13,15]. In this condition, when the patient has a rapid respiratory rate which is equal to the heart rate, the physical findings may resemble pulsus alternans.[13,14]

*Clinical Significance of Pulsus Alternans*

Pulsus alternans occurs most commonly in heart failure and implies left ventricular systolic dysfunction. It is also found in patients with severe myocardial disease due to aortic stenosis, systemic arterial hypertension, coronary atherosclerosis, and dilated cardiomyopathy.[12] This is most likely due to the contribution of these conditions to ventricular dysfunction. Pulsus alternans is often associated with the third heart sound (S3) and disappears with treatment of heart failure.[12] It has however, been described in patients with normal hearts for brief periods during or after an episode of supraventricular tachycardia. Therefore, it should be emphasized that the absence of pulsus alternans does not exclude left ventricular systolic dysfunction[3] and conversely, its presence is not necessarily indicative of disease.[12] Nevertheless, pulsus alternans is a helpful finding in diagnosing and confirming the left ventricular systolic dysfunction. Presence of pulsus alternans indicates a poor prognosis.[13]

## Conclusion

The mechanism underlying the pulsus alternans is yet to be elucidated. However, it is generally accepted that pulsus alternans reflects events occurring at the cellular level rather than the hemodynamics. The favored view at present is that pulsus alternans is associated with $Ca^{2+}$ cycling phenomenon involving the sarcoplasmic reticulum. It is possible that the initiation of the alternans is at the cellular level, but it is further augmented and perpetuated by alteration in the hemodynamics. In the clinical setting, pulsus alternans is associated with heart failure and severe myocardial disease. It may be helpful in diagnosis of left ventricular dysfunction.

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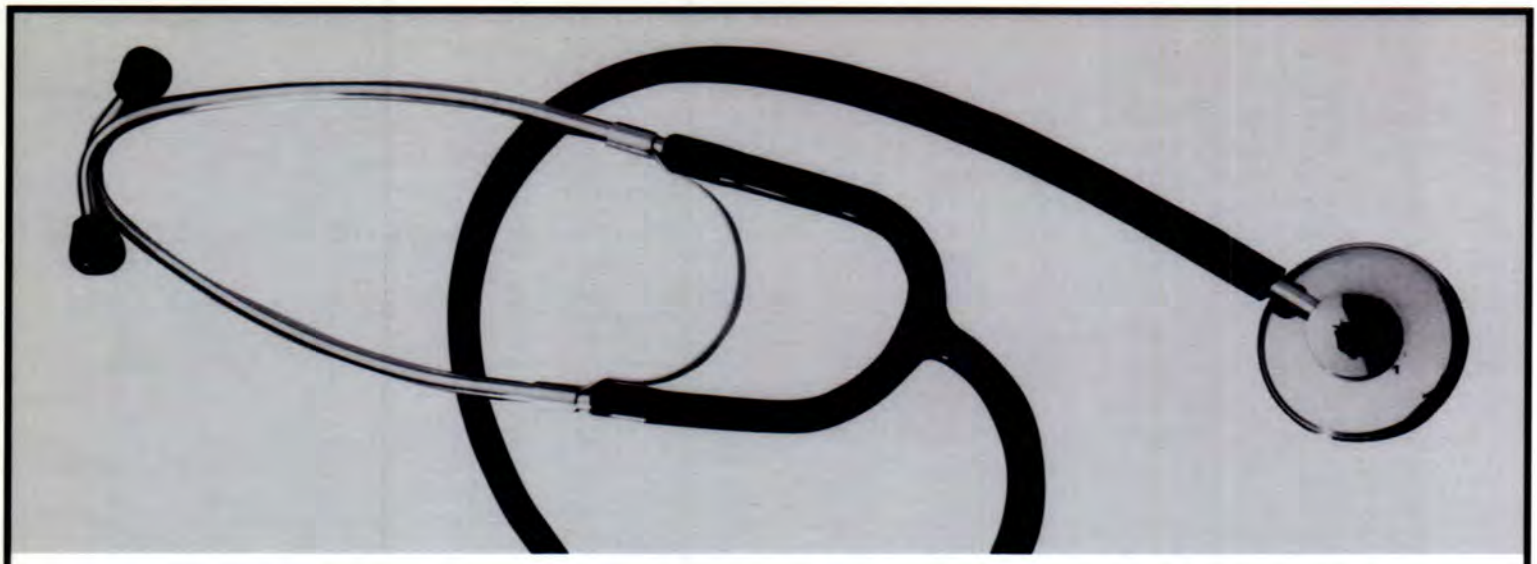

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# HORMONE REPLACEMENT THERAPY FOR CORONARY ARTERY DISEASE IN THE DOMAIN OF EVIDENCE BASED MEDICINE

*By Mandy Schwartz and Natalie Gomperts*

## INTRODUCTION

The field of medicine is evolving such that clinical practice is being guided by the findings of Evidence Based Medicine. This allows physicians to provide the best possible treatment for their patients based on valid outcomes. The use of Hormone Replacement Therapy (HRT) for the reduction of coronary artery disease (CAD) in postmenopausal women is no exception. With the abundant literature on the benefits of HRT, it is surprising to note the low rate of use of HRT in postmenopausal women who are at high risk for CAD or have existing disease. This article postulates reasons for current prescribing practices and patient compliance regarding HRT by examining the current information available to patients and their doctors.

## CORONARY ARTERY DISEASE IN WOMEN

In Canada, coronary artery disease (CAD) is cited as being the leading cause of mortality. In women, deaths due to coronary artery disease outweigh the number of deaths due to cancer and is second only to bone and joint disease in limiting daily activities and decreasing the autonomy of affected women.[1] Overall CAD incidence is higher in men than in pre-menopausal women. However, after the menopause, the incidence in women increases to rates equivalent to men, suggesting the protective role of estrogen in women. A 50 year old woman has a 46% lifetime probability of developing CAD and a 31% chance of dying from heart disease.[2]

## THE BENEFITS OF HORMONE REPLACEMENT THERAPY

Over the past 20 years more than 30 epidemiological studies on hormone supplements and CAD have been carried out. These studies provide evidence of the lower morbidity and mortality from coronary artery disease among users of HRT than among non-users.[3] Observational studies comprise the majority of this literature. These studies demonstrate the risk of coronary artery disease in HRT users as being 30-50% that of non-users.[4] The relative risk among users compared with non-users of HRT is 0.55-0.65 from meta-analyses.4 In terms of secondary prevention of CAD, HRT users have been shown to have had 84% fewer cardiac events than non-users of HRT.[4] Mechanisms of action proposed by these studies include the improvement of endothelial function, alteration of lipid profiles with a reduction in LDL cholesterol and increase in HDL cholesterol, and reduced insulin resistance.[1,5] Guidelines referring to the cardioprotective effects of HRT have been published by the American College of Physicians and the Society of Obstetricians and Gynaecologists of Canada. These guidelines recommend that "women who have coronary artery disease or who are at risk of coronary artery disease are likely to benefit from hormone therapy".[1,2]

## USE OF HORMONE REPLACEMENT THERAPY

Regardless of the biological and epidemiological evidence, as well as published guidelines supporting the benefits of prescribing HRT to those at risk for or who already have CAD, HRT use remains low.[4] An American longitudinal study of 2,500 women, showed that the overall rate of use was only 12.3%.[6] Further, a recent study by Wise et al proposed that HRT use would be higher in a population of postmenopausal women who presented with CAD to an academic cardiology clinic in Toronto between January 1996 and August 1997. These authors based their hypothesis on the current guidelines and literature that supported HRT use for CAD. It was further thought that women at higher risk for CAD would be more likely to use HRT if informed about its potential benefits.6 The results of this study revealed that only 13% of women who had CAD were currently using HRT, while only 22% of those at high risk for CAD were current users.[6]

## REASONS FOR LOW RATE OF HORMONE REPLACEMENT THERAPY USE

In light of the evident cardioprotective benefits of HRT, why does use remain low? Firstly, the perceived threat of breast cancer plays a significant role in determining whether a woman feels confident about starting therapy, regardless of literature findings.[2] Secondly, women may also worry about the side effects of HRT such as irregular bleeding, weight gain and symptoms of premenstrual syndrome.[7] These factors not only deter the start of HRT but may also contribute to early cessation of therapy.

**ABOUT THE AUTHORS**

*Mandy Schwartz and Natalie Gomperts are both second-year medical students at the University of Western Ontario. Mandy Schwartz completed a BSc at York University and is interested in Women's Health. Natalie Gomperts obtained an HBSc in Applied Health Sciences at the University of Waterloo.*

Thirdly, due to the nature of CAD and its modifiable risk factors, physicians may not consider the role of HRT in patient management. The main mechanism of HRT as a cardioprotective agent is its effect on serum lipid levels. Physicians may bias their treatment of abnormal lipid levels towards the use of lipid lowering agents, proven effective by randomized control trials.[7] As well the recommended guidelines are unclear as to dosing regimens, pretreatment investigations, follow up and duration of therapy.[8] This may lead to physician confusion regarding when to prescribe, how long to prescribe for, and whom to prescribe HRT therapy to. Lastly, in this era of evidence based medicine, the greatest possible reason for low prescribing practices of HRT is that the evidence supporting the use of therapy is not robust.[9] Those studies advocating a reduction in mortality and morbidity of CAD in users are based on observational data with inherent methodological flaws.[9]

## LIMITATIONS OF OBSERVATIONAL STUDIES

With the limitations of observational studies, the cardioprotective findings of HRT may be misleading. Many participants taking part in these studies initiated hormone therapy to reduce menopausal symptoms, and prevent osteoporotic fractures, rather than to reduce their risk of CAD.7 These participants tended to be leaner, more health conscious and from higher socio-economic backgrounds than non users of HRT, thus indicating a selection bias in these studies.[7] Due to these factors, occurrence of CAD would be less likely within the studied population.[10] As such, the healthy user effect may have biased the results in favour of a cardioprotective effect of HRT.[7] Furthermore, women who were prone to adverse outcomes, such as a cardiac events despite use of HRT, were more likely to have discontinued therapy. This could lead to an increased prevalence of survivors participating in the observational studies[10]. Due to the controversial nature of the protective findings of HRT, and in the realm of evidence-based medicine, most physicians may only feel confident in prescribing therapy in light of the outcome of Randomized Control Trials (RCT).

## HRT AND RANDOMIZED CONTROL TRIALS

Currently, two North American randomized trials are available for consideration. It is hoped that these experimental studies will help to resolve questions regarding the effect of HRT on cardiovascular risk. The first, the Heart and Estrogen/Progestin Replacement Study (HERS) examined secondary prevention of heart disease in postmenopausal women.[10] The HERS trial randomized 2,763 postmenopausal women with existing heart disease to either an estrogen and progestin intervention or to a placebo group. These women were followed for an average of 4.1 years with main outcome measures including the occurrence of non-fatal MI or CHD death. Secondary outcomes of unstable angina, coronary revascularization, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack and peripheral arterial disease were also included. Results of the study were worrisome in that they showed no overall significant difference between the treatment and placebo groups for primary or secondary cardiovascular outcomes.[10] Further, the trial found a pattern of early increase in the risk of CAD event, although a slight improvement was noted at the four year follow-up.[10] This improvement suggests that follow-up over a longer period of time might reveal a more significant outcome.[10] Unfortunately the trial did not extend its follow-up period so evidence of this effect is not available. Based on these findings, the trial does not recommend HRT for the secondary prevention of CAD, although, it recommends that women already receiving treatment should continue on HRT, due to the potentially favorable long term effects.[10] Finally, the trial did not evaluate the effects of unopposed estrogen therapy for women having undergone hysterectomies, nor did HERS evaluate the cardioprotective benefits of hormone therapy for women at high risk for CAD.[10] Thus, the recommendations made by HERS cannot be extrapolated to these cohorts and should be used with caution. The second study, the Women's Health Initiative (WHI) enrolled 27,500 women in March of 1993 and will not be completed until 2005.[5,7] The study will evaluate the effects of HRT on women without existing CAD. The trial will include both women who have undergone a hysterectomy and are receiving unopposed estrogen therapy and women with an intact uterus receiving combined estrogen and progestin therapy.[10] Results of this study will hopefully resolve some of the issues raised by the HERS trial.

## CONCLUSIONS

With the advent of evidence-based medicine, physicians must wade through conflicting data regarding the prevention of CAD when considering prescribing hormone therapy for their patients. Although the gold standard is the Randomized Control Trial, HERS remains elusive in providing coherent prescribing practices for women at high risk of CAD. Due to the limitations of HERS, publication of comprehensive guidelines will have to wait for the new millennium, when results of further RCTs are available.

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# HEART DISEASE AND GENETICS

By Cecilia Kerner

## Introduction

Heart disease is the most common cause of mortality and morbidity in North America. Due to the large numbers of people affected, there have been substantial resources directed in finding the causes and possible cures for various heart conditions. Throughout this research, many risk factors such as hypertension, smoking, obesity and diabetes have been elucidated. Family history of cardiac disease is also a very important factor used to identify patients who may be at risk. However, until molecular techniques became available, the genetics of how heart disease is passed down within families has been poorly understood. Current technology has now allowed for a search of common variances (polymorphisms) and mutations of genes related to heart disease. So far, several mutations of candidate genes for different cardiac problems have been identified within certain families. More research is still needed to determine how these mutations may cause disease and how to determine the prognosis of severity for a specific mutation. Heart disease is a complex illness and it must be understood that there will never be one responsible gene. The purpose then is to have a bank of responsible genes that can be used to screen individuals early in life in order to implement good lifestyle habits and to monitor those with the genes carefully. The discovery of these genes along with the identification of other risk factors will help in gauging an individual's risk and play an important role in preventive medicine.

## Familial Hypertrophic Cardiomyopathy (FHC)

FHC is an autosomal dominant disease that affects two out of one thousand individuals[1]. It causes an increase in myocardial mass and myofibrillar disarray resulting in fibrosis, abnormally small coronary vessels and arrhythmias[1]. Those who suffer are at a higher risk for sudden and premature cardiac death. There have been several mutations found in contractile proteins, α tropomyosin, troponin T and cardiac myosin binding protein C within families who have FHC[1]. Over fifty mutations have already been identified most of which exhibited a defect in their organization within cells[1]. An example would be a mutation found in a tropomyosin, which is a component of muscle thin filaments and is encoded on chromosome[15]. The mutation involves a substitution of a negatively charged glutamic acid by a neutral glycine near the calcium binding domain[2]. The resulting protein is believed to disrupt assembly and function of the sarcomere structure[2]. Heterozygotes of myosin mutations are not protected because when mixtures of normal and mutant myosins were created an overall decrease in motility and activity occurred[1]. It is believed that the severity of FHC among families depends on the type of mutation. Mutations that alter the amino acid and occur at actin-myosin junctions or at the essential light chain binding domain have a poorer prognosis[1]. Those with mutations where the charge of the amino acid remains the same have been shown to have a higher life expectancy[3]. In studies of large unrelated families sharing the same mutation an association between a specific genotype and survival rate have been shown[3]. However, there is still a range on severity observed within related individuals which confirms that this disease has other factors involved.

**ABOUT THE AUTHOR**

*Cecilia Kerner is a second-year medical student at the University of Western who previously completed a BSc. Honours in Biology/Biotechnology at the University of Ottawa.*

## Coronary Heart Disease (CHD)

Coronary heart disease is usually due to atherosclerosis in the epicardial coronary arteries occluding the arterial lumen and limiting blood flow feeding the heart. When the supply of oxygen cannot meet the myocardial demand due to stenosis, ischemia occurs leading to angina pectoris or myocardial infarction. Family history is a serious risk factor for CHD and many genes are believed to be involved. Since CHD can be combated with drugs or lifestyle changes, screening may become important in both prevention and treatment. It is believed that the genotype may influence CHD risk by interacting with other risk factors such as cholesterol levels and blood pressure[4]. There are several candidate genes that encode proteins related to known risk factors; not all of these genes are mutations but instead are a common variant of a gene. Apolipoprotein E for example has three common polymorphisms, E2, E3 and E4, which influence plasma lipid concentrations[4]. It is a structural component of circulating chylomicrons, VLDL and HDL and affects the fasting plasma lipid levels[5]. E4 produces cholesterol levels higher than average while E2 produced lower levels and may in fact protect individuals from coronary heart disease.

Angiotensin converting enzyme (ACE) converts angiotensin I into the angiotensin II, a vasoconstrictor that may promote vascular smooth muscle growth. It also degrades bradykinin, a vasodilator and inducer of endothelial factors[5]. This implies that concentration itself may contribute to vascular tone, which is critical for healthy coronary arteries. ACE concentrations are stable within an individual and appears to be unaffected by environmental factors suggesting that it must be genetically determined[6]. There are two known alleles: ACE I (insertion) and ACE D (deletion). As Table 1 shows ACE D has the highest ACE concentration; its frequency is found to be higher for patients with angina and MI[6]. A meta-analysis of fifteen studies has also correlated ACE D with an increased risk of MI[4].

Gene products involved in endothelial functions such as fibrinogen, coagulation factors and PAI B1 have been

**Table 1: ACE genotype versus ACE serum levels**

| Genotype | ACE serum levels |
|---|---|
| Homozygous ACE I/I | 299 +/- 49μg/L |
| Heterozygous ACE I/D | 393 +/- 67μg/L |
| Homozygous ACE D/D | 494 +/- 88 μg/L |

implicated in CHD. They have been studied because they are all involved in plaque formation and plaque rupture[7]. Candidate genes include those that determine adhesion of monocytes, expression of vasoactive peptides and vascular proliferation. However, few mutations have been found which cause abnormal protein structure and it is now believed that it is a mutation in the regulatory regions of the genes which is responsible. Such a case has been found in sequences of the promoter of PAI-1 that cause an alteration in transcription causing an increase in atherosclerosis and thrombosis[7].

Homocysteine levels are also involved in endothelial dysfunction by inducing cytotoxic peroxide formation and inhibiting the vasodilator nitric oxide (NO), which can lead to CHD. A commonly found C to T substitution in MTHFR, an enzyme that converts homocysteine to methionine, has a reduced activity and is more unstable than the wild-type protein[8].

### Gene-Gene Interactions

It is well known that activity for one gene is not isolated but is influenced by other genes and their products. Since CHD is a very complicated disease it is likely that there are many gene interactions contributing to the disease. An example was found in a well known study, ECTM (Etude cas-temoin de l'infactus du mycarde), which involved the ACE gene and the angiotensin II type 1 receptor[9]. An A to C substitution in this receptor is asssociated with high blood pressure and those who have both this mutation along with the ACE D allele are at an even higher risk for heart disease[9].

### Genetics and Environment

Heart disease has both a genetic and environmental component. Both of these factors do not work alone but influence one another in determining an individual's predisposition for the illness. It has been discovered that sequences within promoter regions of genes that help determine cholesterol levels (such as LPL, apo A-1 and apo C-III) bind to fatty acids[7]. This might imply that diet not only acts in a direct manner towards influencing cholesterol levels but also indirectly by affecting the expression of involved proteins. Screening for these particular sequences may help to encourage diet modifications.

### Genetics and Drug Therapy

Individuals respond differently to drugs. Some people have more positive results than others even if they are similar in age, gender and body size. Again, genetic variation may be the cause for these differences. Such an example exists with polymorphisms in the apo E gene and the response to anti-hyperlipidemic drugs. It has been found that men with the apo E4 allele do not respond as well to lovastatin, an inhibitor of HMG-CoA reductase, than men with the E2 or E3 alleles[2]. Probucol, another cholesterol-altering drug, however seems to be much more effective for E4 genotypes[4]. The mechanism involved in genetic-drug interactions is still unclear but the implications for this knowledge are very useful. By knowing which drugs are most efficient for a genotype, we will be able to design drug therapies for each individual.

### Conclusion

We are just beginning to find polymorphisms and mutations of genes associated with heart disease and there are probably many more to be discovered. As the Human Genome Project is coming to an end, the search for these genes may become more successful. Even with the knowledge of responsible genes, there are several considerations to be made. Heart disease is very complex and finding absolute markers is not probable. Interactions between lifestyle and environment differ between populations, which means that a particular genotype will not imply equal risk. We will also have to take the genotype of a person into the context of other known risk factors to determine both prognosis and treatment. Screening individuals at risk has been expensive and has

**Table 2: Summary of candidate genes linked to heart disease**

| Gene product | Mutation | Effect | Disease |
|---|---|---|---|
| ACE[4] | ACE D allele | Increase in ACE concentration affecting blood pressure and vascular homeostasis | CHD |
| Apo E[5] | E4 allele | Increase of total cholesterol | CHD |
| PAI-1[7] | Mutation in promoter | Decrease in fibrolytic function | CHD |
| MTHFR[8] | C to T substitution at nucleotide 677 | Hyperhomocystein-emia | CHD |
| AGTFR1[9] | A to C substitution | Hypertension | CHD |
| α tropomyosin[2] | 15 known missense mutations | Abnormal sarcomere | Cardiomyopathy |
| α and β myosin heavy chain[11] | Formation of α/β hybrid (duplication and recombination) | Unknown | Cardiomyopathy |
| β-myosin heavy chain[12] | Substitution of arginine for glutamine | Increase in frequency of sudden death | Cardiomyopathy |

had limited accessibility but now automated assay kits which can identify mutations have been created. They have shown to be sensitive, specific, reproducible and fast with only a few drops of blood or saliva needed[10]. As the expense drops, it will allow both the patient and doctor to treat or change poor habits early in life to improve health and to reduce illness. Aside from lifestyle and drug treatments, gene therapy, which is only at an experimental stage may turn into reality. For example, a transfer of vascular endothelial growth factors to sites of arterial damage, is being delivered during angioplasty to encourage collateral development[4]. Although wide screening raises both ethical and legal issues such as insurance policies, the overall benefit of identifying people at risk for diseases where treatments exist to prevent a premature death is very significant.

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# CORONARY ARTERY BYPASS GRAFTING: THE BASICS

*By Shafie Fazel*

## Introduction

Coronary artery disease (CAD) continues to be the leading cause of morbidity and mortality in the western world. Every year, 1.5 million people suffer a myocardial infarction in the United States. Over one-third of these patients will die. As the baby-boom generation ages, the prevalence, incidence, total mortality, and economic cost of CAD will increase significantly.[1]

## Anatomy, physiology and pathophysiology

The right and left coronary arteries arise from the sinuses of valsalva in the ascending aorta. The right coronary artery (RCA) passes in the right atrioventricular groove, gives rise to several acute marginal (AM) branches, and in 90% of patients, ends as the posterior descending artery (PDA) in the posterior interventricular groove (right coronary dominance). Thus, the main supply of the right side of the heart, including the SA and the AV nodes, and the posterior fascicle of the left bundle branch, is the RCA. The left main coronary artery gives rise to the left anterior descending artery (LAD) and the left circumflex artery. LAD and its diagonal branches supply the anterior and apical aspects of the left ventricle. The perforating branches supply the interventricular septum including the right bundle branch and the anterior fascicle of the left bundle branch. The LAD is a crucial coronary artery in that it supplies the major portion of the left ventricle. The circumflex artery proceeds laterally and posteriorly around the left atrioventricular groove, giving rise to several obtuse marginal (OM) branches. It supplies the postero-lateral and posterior aspect of the left ventricle. In 10% of people, the circumflex artery provides the posterior descending coronary artery (left coronary dominance) and thus the AV node as well.[2]

Coronary blood flow normally approximates 1 mL per gram of myocardium per minute and delivers 0.1 mL of oxygen per gram per minute to the heart. The extraction of oxygen in the average coronary bed is 75% and may increase to 100% in periods of stress. Coronary flow occurs primarily during diastole, and is a function of the difference between systemic diastolic pressure (in the proximal aorta) and left ventricular end diastolic pressure. Coronary arteries possess significant vasodilatory reserve, allowing a three to six-fold drop in the coronary artery resistance in periods of need.[3]

Atherosclerotic disease of the coronary arteries will eventually lead to an imbalance of oxygen supply and demand that prevents adequate perfusion of the myocardial tissue. The resulting ischemia may progress to infarction of the cardiac muscle in the distribution of the respective coronary artery. Chronic arterial insufficiency results in progressive dilatation of the left ventricle subsequent to accumulation of minor infarctions leading to congestive heart failure (CHF) secondary to systolic dysfunction. The sequelae of acute myocardial infarction fall into two categories: i) CHF due to pump failure or a mechanical complication, such as ventricular septal defect, mitral regurgitation due to papillary muscle dysfunction, left ventricular rupture, and cardiac tamponade; and ii) life-threatening ventricular dysrhythmias or heart-blocks.[4]

## Management

The management of coronary artery disease (CAD) may be divided into three progressive stages: i) life-style modifications, ii) medical management, and iii) invasive management. Life-style modifications include exercise, diet, and environmental modifications. Medical management of CAD includes anti-angina medications such as beta-blockers, calcium channel blockers, ACE inhibitors, and anti-platelet agents particularly aspirin. Risk factor management such as blood pressure control in hypertensive patients, cholesterol control in hyperlipidemic patients, and glucose control in diabetic patients are an integral part of the medical therapy for CAD patients. The invasive management of CAD, in patients refractory to medical management, includes two different approaches: i) percutaneous transluminal coronary angioplasty (PTCA) and/or stenting, and ii) direct revascularization of the coronary arteries using venous and arterial conduits: coronary artery bypass grafting (CABG).[1,5]

Patients for whom an invasive intervention is indicated fall into three categories. First category includes patients in whom angina refractory to medical management is present. Second category includes patients in whom the extent of CAD, the ventricular function, and the degree of inducible ischemia on stress testing are such that surgery may improve survival. In this category, CABG is indicated for patients with left main stenosis greater than 50%, three vessel disease with ejection fraction of less than 50%, three vessel disease with ejection fraction greater than 50% and significant ischemia, and one and two vessel disease with extensive myocardial involvement with lesions not amenable to PTCA. Third category includes patients in whom CAD is present concomitantly with other conditions for which open-heart surgery is indicated, such as severe aortic stenosis. In general, PTCA and/or stenting is reserved for patients with simple single-vessel disease, or uncomplicated multivessel disease, providing that the lesions are distinct, and not diffuse.[5]

## Surgical technique of CABG

Conventional surgical revascularization of the heart involves five steps: i) median sternotomy and appropriate dissection through pericardium, ii) administration of heparin, establishment of cardiopulmonary bypass (CPB),

and inducing cardioplegic arrest, iii) anastomosis of saphenous vein grafts (SVG), left internal mammary (LIMA), inferior epigastric, gastroepiploic, and/or radial artery grafts,[6] iv) termination of CPB, and v) wound closure. Establishment of CPB involves right-sided cannulation through the right atrium, and left sided cannulation through the proximal aorta. Thus, the venous return to the right atrium is drained into the heart-lung machine, and after membrane oxygenation, is pumped to the proximal aorta, distal to site of application of a cross clamp. High-potassium cardioplegic solution, administered to achieve arrest of the heart, is infused proximal to the cross clamp, through a small cannula in patients not suffering from aortic regurgitation (AR). In patients with AR, retrograde cardioplegic infusion is established through cannulation of the coronary sinus. The termination of CPB, after the proximal anastomosis of the bypass grafts to the proximal aorta is completed, involves removing the aortic cross clamp, and weaning the ejecting heart from the CPB machine by decreasing the right atrial drainage to the heart-lung machine. Once the heart is able to sustain adequate systemic pressure and cardiac output, the CPB machine is turned off, circulating heparin is reversed with protamine, and the cannulae are removed.[2]

**CABG: Outcome, morbidity and mortality**

Coronary bypass grafting has been shown to significantly improve anginal symptoms in over 90% of patients. Likewise the incidence of myocardial infarction is reduced. Successful revascularization improves resting left ventricular wall motion and enhances exercise ventricular performance. Most importantly, revascularization of the heart is demonstrated to significantly improve survival in patients with CAD. The greatest benefit is evident in patients with severe, multivessel CAD.[7]

Operative mortality has been steadily decreasing. Even during the 1990's operative mortality decreased farther from 3.57% in 1990 to 2.76% in 1997. Advanced age is an incremental risk factor for hospital mortality after CABG (Table 1).[8] The mortality rate also varies with the pre-op status of the patient. Mortality for elective CABG was 3.6%, whereas mortality for salvage CABG was 30.8%. (urgent CABG operative mortality is 5.2%, emergent CABG operative mortality is 9.9%).[8]

**Table 1. Mortality rate by age group**

| Age group | Number of Pts | Operative mortality rate |
|---|---|---|
| 20-50 | 18717 | 1.24% |
| 51-60 | 38923 | 1.42% |
| 61-65 | 25879 | 2.12% |
| 66-70 | 21269 | 2.60% |
| 71-80 | 51040 | 4.07% |
| 81-90 | 8872 | 6.71% |
| >90 | 106 | 11% |

Table 1. As expected, older revascularization patients tend to have higher operative mortality rate. This data is compiled from 1997 U.S. data (N~170000) on the Society for Thoracic Surgeons' web site: www.sts.org

**Table 2: Common complications of coronary artery revascularization**

| Complication | Incidence | Relative risk ratio |
|---|---|---|
| Atrial fibrilation | 19.32% | 1.45 |
| Transient stroke | 0.75% | 1.46 |
| Deep mediastinitis | 0.63% | 3.58 |
| Permanent stroke | 1.69% | 10.84 |
| Ventilation > 24 hrs | 5.87% | 12.66 |
| Dialysis dependant Renal failure | 0.92% | 18.57 |

Table 2. Post-operative morbidity associated with coronary artery revascularization is listed in decreasing rate of incidence. The relative risk ratios (RRR) indicate the higher likelihood of operative mortality. The RRR are statistically significant (P<0.005). The data was compiled from 1997 U.S. data (N~170000) as reported on Society of Thoracic Surgeons' web site: www.sts.org.

The incidence of some of the important morbidity associated with this operation are summarized in Table 2.[8] Respective operative mortality relative risk ratios are listed as well.[8] A major contributor to post-operative morbidity is the need for CPB, which induces a systemic inflammatory response, and can cause neuropsychological and multi-organ dysfunction. The advantages and disadvantages of the CPB machine are discussed below.

CPB machine was developed in the 1950s, and was designed to facilitate cardiac surgery. It's advantages are numerous. The heart is arrested and deflated, the surgical field is blood-less, and the surgeon is able to perform the operation efficiently, accurately, and quickly.[2] Most importantly, the surgeon supports the patient's circulation using the CPB machine while corrective surgery is being performed.

Disadvantages of CPB machine are three-fold. First, priming of the bypass circuit results in hemodilution and post-operative water retention, both of which can increase the post-operative length of stay. Second, circulation through incompletely bio-compatible CPB cannulae, tubing, and membrane oxygenator, results in damage to blood elements, a systemic inflammatory response (SIRS), and a post-operative hypocoagulable state. Third, manipulation of a diseased ascending aorta can generate a shower of micro and macro-emboli that may cause cerebrovascular accidents (CVA), and/or neuropsychological dysfunction.[2]

The occurrence of CVAs in heart-surgery patients remains a significant draw-back to this successful operation. To avert embolization of atherosclerotic plaques, surgeons routinely examine the aorta carefully to locate a healthy segment for cannulation.[2] Even with this precaution, the rate of a cerebral event is approximately 8% for patients over the age of 70, and 16% for patients over the age of 80.[9,10] Recently, aortic filters have been manufactured to capture emboli shed during the cannulation of the aorta. The efficacy of such filters is currently under study. Beating-heart bypass operations, if feasible, can reduce the risk of CVAs by avoiding aortic manipulation[11] (discussed below).

**Evolution of CABG**

In the hope of decreasing operative mortality and morbidity, minimally-invasive techniques of CABG have evolved during the past three to four years. These techniques have involved the use of a smaller incision, and/or attempting to bypass vessels without the support of the CPB machine. To summarize, the following protocols have been developed: i) OPCAB, ii) MIDCAB, iii) Port-access, iv) ministernotomy CAB, and most recently v) closed-chest CAB via endoscopic methods.

The OPCAB operation[12-16] involves a full-length median sternotomy, but the bypass is attempted on the beating heart using stabilizing instruments. In this procedure, the surgeon does not have full access to the posterior aspect of the beating heart. As well, manipulations of the beating heart may result in significant hemodynamic instability by interfering with venous return to the heart. Early studies indicated that OPCAB is as safe as conventional CABG in selected patients. Reported OPCAB operative mortality ranges from 1.0% to 2.5%.[12-16] As a result, the number of OPCABs done are dramatically increasing.

The MIDCAB[17-23] operation most commonly involves the grafting of LIMA to LAD through left anterior thoracotomy, or RIMA to RCA or PDA through a right anterior thoracotomy, on a beating heart. Other arterial conduits, such as the inferior epigastric and the gastroepiploic artery have also been used. Direct anastamosis of the SVG and radial artery to the ascending aorta is not possible through a small thoracotomy incision. If the use of such grafts is indicated, the SVG and radial artery can be anastamosed to the LIMA, and then to a coronary artery as a "T" graft. Recently a lateral MIDCAB[24] approach has been attempted to bypass OM branches of the circumflex artery. The SVG is proximally anastomosed to the descending aorta in this procedure. The lateral MIDCAB operation does not allow the surgeon to have access to the LAD and proximal RCA. Early concerns existed that anastomosis carried out on a beating heart, through a limited-access incision, may not be technically precise, and may have a high occlusion rate. Several studies, however, have shown that graft patency after revascularization using the LIMA to LAD anastomosis is comparable between conventional CABG[25-30] and MIDCAB[17-23] (graft patency > 90%). Furthermore, the risk of CVAs has been shown to be decreased in MIDCAB as compared to conventional CABG.11 Growth in the number of MIDCAB procedures, however, has been relatively flat because MIDCAB is mainly reserved for the surgical therapy of single vessel disease. As such, it competes more or less directly with PTCA.

Another approach, the Port-access approach[31-36] involves establishment of CPB and arrest of the heart by using the femoral vessels for right and left sided cannulation. The heart is arrested with a cold blood cardioplegic solution delivered through the central lumen of a balloon occlusion catheter in the ascending aorta, and cardiopulmonary bypass is maintained with femorofemoral bypass. This is followed by a left anterior thoracotomy to access the coronary arteries. With the heart arrested, the minithoracotomy affords enough room for the surgeon to bypass multiple vessels on a deflated, easily manipulated heart. Early studies indicate that operative mortality and graft patency are comparable to conventional CABG.[32-36] However, this approach is criticized for its prolonged CPB times, and the small yet definite risk of retrograde aortic dissection, particularly if the femoral or iliac arteries are diseased.

The ministernotomy CAB[37] approach is essentially identical to the conventional CABG procedure with the difference that the entry wound is smaller. That is, with a smaller incision, the surgeon has access to all coronary arteries with full CPB support. The sternotomy is made inferior to the attachment of the third rib to the sternum. The ministernotomy CAB is still in its infancy. Dr. Doty and colleagues[8,37] in Salt Lake City have reported this operation on 77 patients so far, with an average of 4.1 grafts per patient (comparable to conventional CABG). In their initial series, they reported an operative mortality of 2.6%. It is not clear whether post-operative pain after a ministernotomy is significantly less than after a full median sternotomy. It remains to be seen if this procedure develops its own niche in patients with a particular concern for cosmetics.

The closed chest CAB involves insertion of surgical instruments and a robot-controlled video camera through small 5 to 10 mm incisions in the chest wall. Bypass may

**Table 3. Pre-operative and intra-operative factors with significant contribution to post-operative mortality**

| Pre-op factors | Relative risk ratio |
|---|---|
| Cardiogenic shock | 7.89 |
| Prior MI < 6 hrs vs no MI | 6.12 |
| Resuscitation | 5.13 |
| Renal failure requiring dialysis | 3.47 |
| Renal failure | 3.45 |
| Prior MI in 6-24 hrs vs no MI | 3.45 |
| PTCA to OR < 6 hrs | 3.32 |
| Pulmonary hypertension | 2.92 |
| CHF | 2.87 |
| Prior CAGB | 2.66 |
| Arrythmia | 2.3 |
| Peripheral vascular disease | 2.22 |
| Immunosuppressive therapy | 2.13 |
| Prior non-cardiac operation | 2.03 |
| **Intra-op factors** | |
| Intra-op IABP | 9.57 |
| Cryoprecipitate transfusion | 5.19 |
| FFP transfusion | 4.48 |
| Platelet transfusion | 4.11 |
| RBC transfusion | 3.7 |
| Inotropes leaving OR | 2.88 |
| Anti-arrythmics leaving OR | 2.87 |
| Ventricular pacing | 2.32 |

Table 3. Pre-operative status and intra-operative factors have predictive value in determining the risks of operative mortality. Only statistically significant (P<0.005) relative risk ratios above 2.0 are compiled in this table. The data is obtained from the 1997 U.S. data (N~170000) on the Society for Thoracic Surgeons' web site: www.sts.org.

**Plate 1. Invasive management of CAD. The rate of PTCA and CABG over the last two decades.**

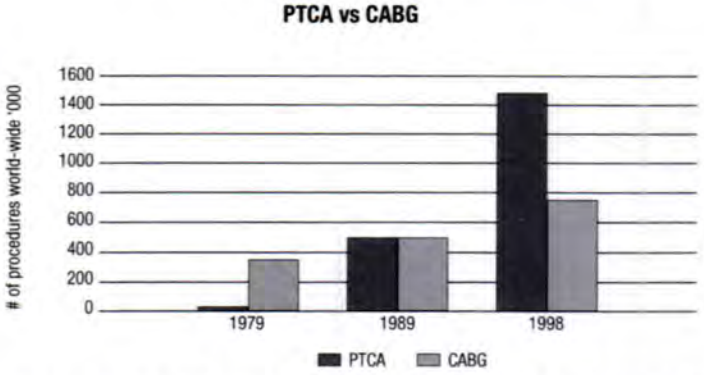


Plate 1. Whereas the number of surgical revascularization of the heart has steadily doubled over each decade, the number of angioplastic procedures has grown exponentially in the past 20 years. PTCA is becoming progressively effective when combined with stent placement and anti-platelet drug (Abciximab) therapy. For complex and diffuse coronary artery disease, however, the invasive procedure of choice remains surgical bypass grafting.

be attempted either on an arrested heart, using the Port-access approach, or on a beating heart. The Port-access, closed chest CAB operation has been reported in France and Germany in 4 cases.[38,39] In all four cases, the post-operative course has been uncomplicated, and LIMA grafts have been patent. The beating heart, closed chest CAB has been successfully performed on one patient so far. Dr. Boyd at the University Campus of the London Health Sciences Centre, performed the first robotically-assisted, closed chest, beating heart CAB on Sept 24 of this year. The post-operative course for this patient was uncomplicated, and a post-operative angiogram showed a perfect LIMA to LAD graft.

## Closing

As 21st century approaches, the future of cardiac surgery is clearly headed toward minimally invasive procedures. Closed chest CABG is a newly developed procedure, and its advantages and disadvantages need to be elucidated in multi-centre studies. It, however, provides an exciting opportunity for the cardiac surgeon to significantly reduce the morbidity associated with full sternotomy, on-pump bypass surgery. Although minimally-invasive operations may be technically very demanding, they provide the surgeon with the satisfaction of having achieved the same excellent outcome of conventional CABG, with only slightly more bodily invasion than a PTCA.

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# LIPITOR*

ATORVASTATIN CALCIUM

*EFFICACY TO REACH TARGET THE FIRST TIME*

**LIPITOR***

(Atorvastatin Calcium)

10 mg, 20 mg and 40 mg tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

***ACTIONS AND CLINICAL PHARMACOLOGY***

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins.

Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG Co-A reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

***INDICATIONS AND CLINICAL USE***

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa),
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly-to-moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (>11 mmol/L).

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = total-C - [(0.37 x (TG) + HDL-C)]

LDL-C (mg/dL) = total-C - [(0.2 x (TG) + HDL-C)]

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

***CONTRAINDICATIONS***

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

***WARNINGS***

**Pharmacokinetic Interactions**

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

**Hepatic Effects**

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

**If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.**

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

**Muscle Effects**

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of a pharmacokinetic study with erythromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

***PRECAUTIONS***

**General**

**The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.**

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

**Effect on the Lens**

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

**Effect on Ubiquinone ($CoQ_{10}$) Levels**

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patents with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

**Effect on Lipoprotein (a)**

**In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).**

**Hypersensitivity**

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

**Use in Pregnancy**

**LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).**

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

**Nursing Mothers**

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

**Pediatric Use**

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

**Geriatric Use**

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

**Renal Insufficiency**

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects: PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

**Endocrine Function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

**Drug Interactions**

**Concomitant Therapy with Other Lipid Metabolism Regulators:** Combined drug therapy should be approached with caution as information from controlled studies is limited.

Friedewald, WT et al. *Clin Chem* 1972; 18(6): 489-502.

**Bile Acid Sequestrants:**

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

**Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid):** Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

**Coumarin Anticoagulants:** LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

**Digoxin:** Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.

**Oral Contraceptives:** Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethindrone and 35µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

**Antacids:** Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

**Cimetidine:** Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

**Cytochrome P-450-mediated Interactions:** Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (including erythromycin and clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant nefazodone may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In a study with healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

**Antipyrine:** Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

**Erythromycin:** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and erythromycin, a known inhibitor of CYP 3A4 (see WARNINGS, Muscle Effects).

**Other Concomitant Therapy:** In clinical studies, LIPITOR was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

**Patients with Severe Hypercholesterolemia:** Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

**Drug/Laboratory Test Interactions**

LIPITOR may elevate serum transaminase and creatine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

***ADVERSE REACTIONS***

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

**TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo Controlled Clinical Trials**

| | Placebo % (n=270) | LIPITOR % (n=1122 ) |
|---|---|---|
| **GASTROINTESTINAL** | | |
| Constipation | 1 | 1 |
| Diarrhea | 1 | 1 |
| Dyspepsia | 2 | 1 |
| Flatulence | 2 | 1 |
| Nausea | 0 | 1 |
| **NERVOUS SYSTEM** | | |
| Headache | 2 | 1 |
| **MISCELLANEOUS** | | |
| Pain | <1 | 1 |
| Myalgia | 1 | 1 |
| Asthenia | <1 | 1 |

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports of severe myopathy with or without rhabdomyolysis have been reported (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated cases of thrombocytopenia and allergic reactions (including urticaria, angioneurotic edema and anaphylaxis) that may have no causal relationship to atorvastatin, have also been reported.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

***SYMPTOMS AND TREATMENT OF OVERDOSAGE***

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

***DOSAGE AND ADMINISTRATION***

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association (AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia

The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy.

Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of 4 weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

**Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.**

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

**TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia**
(Mean Percent Change from Baseline)[a]

| Lipid Parameter | LIPITOR Dose (mg/day) | | | |
|---|---|---|---|---|
| | 10 (N=22) | 20 (N=20) | 40 (N=21) | 80 (N=23) |
| Total-C: 7.1 mmol/L[b] (273 mg/dL)[b] | -29 | -33 | -37 | -45 |
| LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b] | -39 | -43 | -50 | -60 |

[a]Results are pooled from 2 dose-response studies.
[b]Mean baseline values.

**Severe Dyslipidemias:**

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

**Concomitant Therapy**

See PRECAUTIONS, Drug Interactions.

**Dosage in Patients With Renal Insufficiency**

See PRECAUTIONS.

***PHARMACEUTICAL INFORMATION***

**Drug Substance**

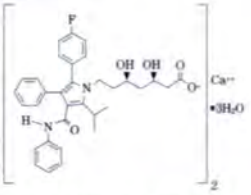
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$

Molecular Weight: 1209.42

Structural Formula:




Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

**Tablet Composition:**

Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

**Stability and Storage Recommendations:**

Store at controlled room temperature 15 to 25°C.

***AVAILABILITY OF DOSAGE FORMS***

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

**10 mg:** White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

**20 mg:** White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

**40 mg:** White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

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# CHLAMYDIA PNEUMONIAE: A POSSIBLE CAUSE OF ATHEROSCLEROSIS

By Sandy Widder

## INTRODUCTION

*Chlamydia pneumoniae* is a Gram negative obligate intracellular bacterium. The organism has a biphasic life cycle consisting of a small, dense elementary body and a larger, metabolically active cell called the reticulate body. The elementary body is the infectious form of the agent and is usually transmitted between humans via aerosol drops. The reticulate body is the vegetative form and divides via binary fission to form inclusion bodies in the host cell.[1] *C. pneumoniae* is responsible for a variety of respiratory syndromes, such as: pneumonia, pharyngitis, bronchitis, asthma and chronic obstructive pulmonary disease.[2] *C. pneumoniae* infections are common and it is estimated that 50 - 70% of adults are seropositive.[1] In recent years, this bacterium has been identified as a possible cause of atherosclerosis.

Atherosclerosis is the principal underlying cause of coronary artery disease. The atherosclerosis develops as a response to injury to the endothelium and smooth muscle of the arterial wall.[3,4]

Endothelial injury leads to the adherence of platelets and activation of macrophages which migrate to the subendothelium.[3,4] The macrophages ingest low density lipoprotein and become foam cells.[3,4,5] Release of growth factors, by the macrophages and platelets, leads to the proliferation of smooth muscle cells and secretion of extracellular matrix.[3,4] The earliest lesions are fatty streaks which in turn develop into fibrous plaques (a fibrous cap surrounding a lipid rich core), and eventually become calcified.[4,5] These atherosclerotic plaques decrease arterial lumen diameter and may lead to total obstruction. If there is ulceration or rupturing of the plaque, a thrombus may form as a result of platelet adherence and aggregation. If the thrombus continues to increase in size, the already narrowed lumen may become partially or fully blocked, thus precipitating ischemia.[3,4] It has been suggested that *C. pneumoniae* infection of endotholelial or smooth muscle cells of vessel walls results in local inflammation and fibrosis and subsequent atheroma formation.[6] Chronic infection with *C. pneumoniae* may also stimulate the production of pro-inflammatory cytokines, thus increasing the risk of cardiovascular disease.[7]

**ABOUT THE AUTHOR**

*Sandy Widder is a second-year medical student at the University of Western Ontario who previously completed an HBSc in zoology at the University of Calgary.*

## INFECTION WITH C. PNEUMONIAE AND ATHEROSCLEROSIS

*C. pneumoniae* first became associated with atherosclerotic disease when studies demonstrated increased titres of immunoglobulin G (IgG) and IgA antibodies in the serum of males who had coronary artery disease or who suffered acute myocardial infarctions, compared to controls.[8]

Saikku et al., demonstrated that those individuals who possessed elevated titres of antibodies had twice the risk of coronary artery disease.[9] In addition to seroepidemiological studies, other experiments have found *C. pneumoniae* within atheromatous lesions via immunohistochemistry and polymerase chain reaction[10], electron microscopy[11], and culturing techniques.[12]

The presence of *C. pneumoniae* in atherosclerotic lesions, however, does not produce enough evidence to indicate a distinct role, and there is debate as to whether the presence of *C. pneumoniae* is causative, contributory, or merely coincidental. Animal studies have contributed greatly by providing further evidence on the role of *C. pneumoniae* in the development of atherosclerosis. Laitenen at el., using New Zealand white rabbits, demonstrated that after intra-nasal or tracheal inoculation of *C. pneumoniae*, 2/3 demonstrated atherosclerotic-like changes in the aorta, while no lesions were found in the controls.[13] Additionally, treatment with antibiotics following infection of rabbits prevents the development of atheromatous lesions. It has also been demonstrated that *C. pneumoniae* accelerates the atherosclerotic process in the aortic arches of apolipoprotein-E deficient mice.[14]

## CLINICAL TRIALS

The possibility of *C. pneumoniae* producing arterial inflammatory changes has led to several clinical trials utilizing macrolide antibiotic therapy as a means of treating atherosclerosis. In rabbits, weekly treatments with azithromycin after exposure to *C. pneumoniae*, prevented the acceleration of atherosclerosis.[13] There have also been human clinical trials which demonstrated a fivefold reduction in adverse cardiovascular outcomes in patients receiving azithromycin[15], and a reduction in future cardiac events from 10% to 1% using roxithromycin.[16] Unfortunately, the numbers used in the human clinical trials were small, and therefore the results must be interpreted with some caution.[2]

## CONCLUSION

Although a direct causal relationship has not been established between *C. pneumoniae* and atherosclerosis, recent scientific evidence has strengthened the likelihood that *C. pneumoniae* may initiate or worsen atherosclerotic

disease. The results of clinical trials using macrolide antibiotics have been especially encouraging; however, further research is needed. There have not been any large clinical trials corroborating atherosclerotic improvement with antibiotics. In addition, one needs to establish that the optimistic results are not the consequence of drugs acting in a non-antimicrobial fashion on other inflammatory mechanisms.[2]

Finally, one must look at the consequences of using antibiotics within the community; the widespread use of antibiotics may selectively increase drug-resistant bacteria. Should *C. pneumoniae* be an infectious cause of atherosclerosis, one would be able to identify and treat those at risk. In the future, one might be able to eradicate atherosclerosis by means of a simple pill!

**ACKNOWLEDGMENTS**

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# THERAPEUTIC MYOCARDIAL ANGIOGENESIS: PROSPECTS FOR GENE THERAPY

*By Warren Ball, BSc., MSc. and David G. Almond, MD, FRCPC*

## INTRODUCTION

Ischemic heart disease remains the leading cause of mortality and morbidity in the Western world. Therapeutic approaches to the management of patients with chronic myocardial ischemia are currently aimed at reducing disease progression via risk factor modification, reducing myocardial oxygen demand and cardiac events with medication or increasing blood supply to compromised myocardium by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). However a significant portion of patients are refractory to medical therapy and are not candidates for PCI/CABG. The growth in our understanding of molecular signaling pathways in blood vessel formation has led to research aimed at stimulating growth and development of new collateral vessels that will form endogenous bypass conduits, termed therapeutic angiogenesis. This review outline the impetus for angiogenesis in the myocardium and will describe the molecular and cellular events of angiogenesis, including the key regulatory angiogenic factors. Finally, as the ability to induce myocardial angiogenesis would have dramatic impacts in cardiovascular medicine, progress into the field of therapeutic angiogenesis will be summarized.

### Myocardial Requirements for Angiogenesis

The three primary stimuli believed to stimulate angiogenesis are: 1) mechanical factors[1], 2) hypoxia[2], and 3) inflammation[3]. Mechanical factors, such as increased shear stress associated with increased blood flow, may induce angiogenesis by disrupting the endothelial surface, resulting in the release of proteases and/or angiogenic factors.1 The homeostasis of myocardial oxygenation is regulated within narrow limits by moment-to-moment adjustments in coronary artery tone, which in turn controls blood flow in direct proportion to cardiac oxygen demand.[4] This is true even under conditions of stress, for example during exercise or in early stages of cardiac disease. However, the vasodilatory reserve of coronary arteries is limited and, particularly in the face of severe atherosclerosis, when oxygen demand exceeds supply, hypoxia ensues, impeding myocardial function. Fortunately the heart is equipped with a long-term homeostatic mechanism for maintaining myocardial oxygenation in the face of hemodynamic or metabolic stresses; chronic hypoxia triggers neovascularization.[5] Inflammation also represents an important modulator of myocardial angiogenesis. Following infarction, myocardial necrosis is accompanied by the influx of lymphocytes and macrophages with subsequent release of angiogenic factors.[6] These mechanisms are by no means mutually exclusive and the continual interaction of each likely occurs in vivo.

### Cellular Components of Angiogenesis

A number of components of the stable vessel are potentially involved in active neovascularization.[7] Most prominent are the endothelial cells (ECs). Once thought to be passive liners of the microvasculature, these cells are now recognized as a composite active endocrine organ. Pericytes sit adjacent to the endothelium and contribute to the regulation of vessel size through adjustments in muscular tone and may check the proliferation of ECs.[7]

Providing structural integrity to the thin walled capillary are the basement membrane (BM) and the extracellular matrix (ECM). The arrangement and composition of the ECM appears to be vital to the angiogenic response.[7] For example, collagen modulates EC proliferation and motility, while heparin sulphate proteoglycans (HSPGs) bind various growth factors, thereby serving as a repository of angiogenic modulators in anticipation of appropriate stimuli.[8] Macrophages and platelets may also contribute to angiogenesis, releasing a host of factors capable of modulating the angiogenic response.

### Angiogenic Growth Factors

Early investigative work into the mechanism of angiogenesis arose from oncology research, as it was observed that tumors could be implanted into an avascular region, such as the cornea, and induce the in-growth of new capillaries. Thus, the impetus became the identification of the released diffusible activators capable of stimulating the relatively quiescent vasculature to proliferate. A number of potent angiogenic factors have been discovered, including basic and acidic fibroblast growth factor (bFGF and aFGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β)[9-11], insulin-like growth factor-I (IGF-I)[12], hepatocyte growth factor (HGF)[13,14], tumor necrosis factor-alpha (TNF-α)[15], platelet activating factor (PAF)[13], nitric oxide (NO)[16,17], adenosine[18-20], and angiopoietin[21].

**ABOUT THE AUTHORS**

*Warren Ball is a second-year medical student at the University of Western Ontario. Prior to entering medical school he earned an Honours BSc. in Life Sciences at Queen's University and an MSc. in the Cardiovascular Science Collaborative Program at the University of Toronto. David Almond is the Director of Invasive Cardiac Services of the London Health Sciences Centre and an Assistant Professor of Medicine at the University of Western Ontario.*

**An Integrated View of Angiogenic Regulation**

A number of different stages have been proposed for the process of angiogenesis[7,22]; however, in reality angiogenesis is a cascade of overlapping events; any division therein is mainly didactic. Figure 1 depicts a speculative cascade for the molecular control of angiogenesis based upon the evidence accumulated to date. A step-by-step description of this diagram follows:

1. An initiating stimulus, such as hypoxia or ischaemia, is required to activate the quiescent vasculature.
2. An upregulation of EC VEGF[23,24], bFGF[25] and NO[26,27] gene expression ensues.
3. These factors act via autocrine and paracrine pathways to: (a) increase the permeability and dilatation of the vessel wall, (b) induce the release of proteolytic enzymes[28,29], including serine proteases, urokinase-type and tissue-type plasminogen activators (uPA, tPA), matrix metalloproteinases, and collagenases which dissolve the local BM and ECM and (c) stimulate EC motility.
4. (a) The degredation of the ECM also releases (activates) sequestered VEGF and bFGF bound to HSPGs in the ECM. (b) In the heart, cardiomyocytes may release adenosine, VEGF, bFGF, and NO in response to injury, while increases in blood flow (shear stress) and oxygen consumption in normal or border-zone tissue surrounding an infarct may also stimulate the release of angiogenic factors.
5. The angiogenic factors released from the ECM, ECs and HSPGs, in addition to co-factors (heparin and plasmin) provided by the extravasation of plasma, provide the chemotactic impetus for EC migration away from the vessel wall and into ischemic myocardium. ECs subsequently differentiate, change shape and adhere to one another to form the lumen of a new capillary.[7]
6. VEGF, bFGF and NO are chemotactic for macrophages/monocytes and induce these cells to release of a host of angiogenic modulators. Fibroblasts, too, potentiate EC proliferation and migration by releasing HGF into the extracellular milieu and initiating the in situ biosynthesis of PAF, VEGF and HGF itself.[13]
7. In addition to their structural role, pericytes may activate TGF-β[31], which subsequently inhibits EC proliferation11 and promotes differentiation and formation of tubules[32]. These tubes fuse and coalesce into loops and blood circulates through the new vascular bed. Only now does de novo BM synthesis begin, and as a result the immature vessel is initially relatively leaky.
8. IGF-I also contributes to the differentiation and morphogenetic phases of angiogenesis by shifting the proteolytic balance back to homeostasis and, along with TGF-β, by stimulating the fibroblast synthesis of BM/ECM components.[10]

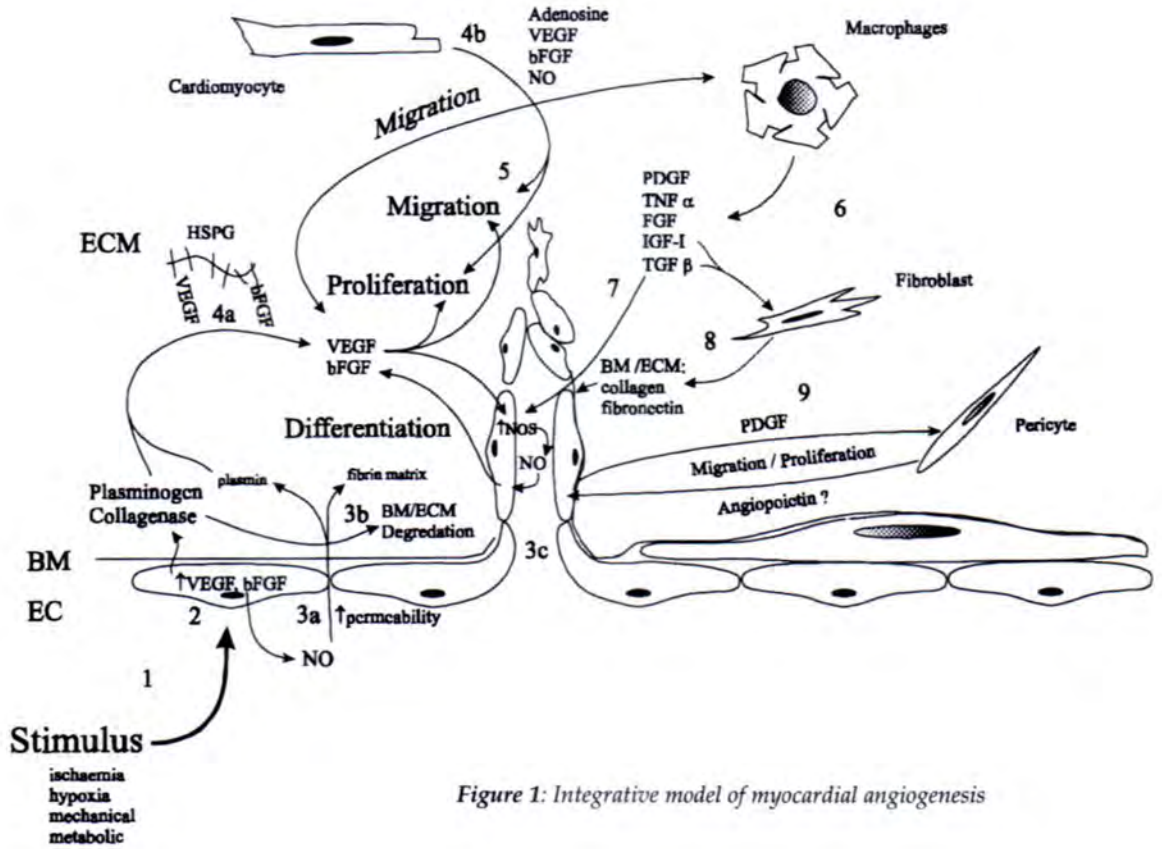


*Figure 1: Integrative model of myocardial angiogenesis*

9. Fibroblasts and pericytes are attracted to the forming vessel, secreting matrix components and providing structural and functional support.[7] Given its apparent role in vasculogenesis, it has been suggested that angiopoietin may be involved in the control of pericyte proliferation and migration in this stage of angiogenesis.[21]

The angiogenic cycle is complete.

**Therapeutic Angiogenesis**

In the heart, the extent of coronary collateral vascularization (blood flow) is a determinant of infarct size, the amount of surviving viable myocardium and, thereby, prognosis in patients suffering an acute myocardial infarction.[33] However, often thrombus formation proceeds faster than collateral development, which may require days to weeks.[34] Therapeutic induction of myocardial angiogenesis immediately following a myocardial infarct offers the hope of minimizing or preventing the resultant cardiomyocyte cell loss, fibrosis, loss of function, wall thinning and, ultimately, heart failure. Even more efficacious would be therapeutic induction of coronary collateral development in the ischaemic myocardium of patients with coronary artery disease before progression to infarction. To date, research has focused on the most prominent of the identified angiogenic growth factors in the development of therapeutic angiogenic strategies - VEGF and the FGFs.

Evidence that administration of bFGF[35] and VEGF[36] could therapeutically induce angiogenesis was first accomplished in a rabbit model of hind-limb ischemia. Extending this work to the myocardium, intracoronary administration of bFGF[37] of VEGF[38] was shown to enhance collateral perfusion and myocardial vascular density in response to myocardial ischaemia in a canine model. Similarly, exogenously administered bFGF improves coronary flow and reduces infarct size in compromised porcine myocardium[39]. However, despite the efficacy of systemic pharmacological interventions[40,41], there is concern over observed systemic activity of administered growth factor peptides.

Gene therapy may circumvent this by providing continuous, local expression of angiogenic agents. Potential delivery vectors include plasmids, viral vectors (adenoviruses or herpes simplex viruses), or cells. Again utilizing the rabbit model of hind-limb ischemia, Isner's group has demonstrated augmented collateral development[42] following percutaneous application of plasmid VEGF165,which had been applied to a hydrogel polymer coating of an angioplasty balloon[43]. Use of an adenoviral vector expression VEGF has also been shown to improve myocardial perfusion and function in a porcine model.[44]

The encouraging results in animal models have resulted in the initiation of clinical trials of therapeutic angiogenesis. Proof of concept for the clinical benefit of angiogenic growth factors was initially documented in patients with critical limb ischaemia.[45,46] Recently, aFGF has been used for the first time in patients undergoing elective CABG.[47] The growth factor was injected into the myocardium distal to an internal mammary artery - left anterior descending (LAD) anastomosis and close to the LAD in a region containing additional stenoses of the LAD or one of its diagonal branches. Angiography twelve weeks later demonstrated capillary formation around the site of injection sprouting from the proximal part of the coronary artery and rejoining the distal parts of the vessel. Isner has also undertaken a phase I clinical trial evaluating therapeutic angiogenesis in patients with severe ischaemic cardiac disease who are not candidates for mechanical revascularization, including those with occlusion of vessels too small to be bypassed, those without conduits, and those who are not surgical candidates because of concomitant disease. However, this study evaluates the safety and efficacy of direct injection of naked plasma VEGF DNA as sole therapy for severe (functional class 3 or 4) exertional angina.[48] Early results from five patients reported that all patient experienced marked symptom improvement and/or objective evidence of increased myocardial perfusion, as evaluated by angiographic and single photon emission computed topography (SPECT)-sestamibi studies, between 30 and 60 days following the procedure. Similarly, bFGF and VEGF, delivered by intracoronary injection, have entered into a phase I trial in ischaemic myocardium not amenable to CABG.[6]

While early results suggest that application of angiogenic growth factors to the myocardium is safe and may lead to decreased symptoms and increased myocardial perfusion in selected patients, significant questions remain. Optimizing the anatomic site, number and dose of intramyocardial injections will require further work. The appropriate formulation or vector also remains to be determined. Recombinant VEGF protein has also shown to be efficacious for the induction of limb and myocardial angiogenesis in pre-clinical and preliminary clinical investigations[47] and the adenoviral VEGF vector, shown to increase myocardial perfusion and function in porcine myocardium, is now being tested in human subjects[44].

Perhaps most significantly, minimally invasive methods of growth factor introduction will need to be developed to permit proper scientific studies that include randomization of human subjects versus placebo. Current clinical studies involving VEGF require a mini-thoracotomy. The availability of a catheter based system to deliver reliable percutaneous myocardial gene delivery may solve this issue and is currently under investigation[49]. Recent work has also investigated the pericardial space as a potential site for angiogenic factor delivery and/or expression.[50,51] Cardiomyocyte transplantation into scarred myocardium has already been shown to restore heart function in rats[52] and, in combination with gene therapy, offers a means of replacing fibrous scar with functional cardiomyocytes while simultaneously inducing angiogenesis to salvage surrounding viable myocardium and ensure adequate oxygenation to the transplanted cells.

**Summary**

Adequate blood supply is a condition for myocardial survival and function. Thus, vascular growth is under tight regulation by a multifactorial cascade balancing the initiation and down-regulation of angiogenesis. The

presence of growth factors in the myocardium alone is not sufficient to permit angiogenesis; additional stimuli—chemical, molecular, or mechanical—are required. Research has demonstrated that the addition of specific growth factors can initiate coronary collateral development in the presence of myocardial ischemia. However, it remains to be fully elucidated whether angiogenesis can be efficaciously induced through the introduction or up-regulation of a single vital growth factor or whether the altered expression of multiple factors is necessary to achieve therapeutic results. Thus, future studies must be aimed at establishing the optimal angiogenic factor(s), dose and route of administration for extrapolation to the clinical setting. Gene therapy is currently the focus of therapeutic angiogenic research and results from early clinical trials offer the promise of minimally invasive myocardial revascularization for patients with severe ischemic heart disease.

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# A LITERATURE REVIEW OF EXTRAHEPATIC BILE DUCT CANCER

By A.K. Sahajpal and W. Davies MD

## Introduction

Extrahepatic bile duct (EHBD) carcinoma is an uncommon malignancy with overall five year survival rates less than 5%[1]. Lesions are frequently small, making diagnosis difficult, and they are often locally invasive at the time of presentation making resection impossible[2]. Tumours usually spread within the bile ducts and, locally, they may invade the hepatic artery, portal vein and liver parenchyma[3]. Surgical resection offers the only chance for long-term survival[1-11]. Surgical cure and prognosis are based primarily on the stage of the tumour at the time of diagnosis. Anatomical location of the lesion, morphological type, and grade of the tumour also affect prognosis[4]. Overall, the five year survival with surgical resection is less than 30%.

These tumours arise from epithelial cells lining the major extrahepatic bile ducts. The majority of tumours appear histologically and microscopically similar[5]. Generally, tumours are mucin-producing adenocarcinomas. Three anatomic divisions are recognized for tumour classification: (1) Upper third, involving the hilar region and confluence of right and left hepatic ducts - this type of EHBD tumour is also known as a Klatskin tumour; (2) distal to the junction of cystic duct and the superior border of the pancreas (middle third); and (3) the lower third at the distal end of common bile duct[2,11].

Location of the tumour is responsible for differing survival rates[2,11]. Lesions of the distal third are most often curable with resection, whereas Klatskin tumours (upper third lesion) are often invasive and unresectable at the time of presentation, and have low survival rates with resection[2,11]. Unfortunately, the confluence of the hepatic ducts constitutes the location of approximately one-half of all malignant bile duct cancers[6-10,12-27].

Morphologic subtypes include papillary/polypoid, and sclerosing tumours. These lesions can be well, moderately, or poorly differetiated[2]. Papillary lesions have a significant long-term survival advantage compared to sclerosing lesions[11]. In EHBD cancers, local invasion, lymph node metastases and the status of the surgical margins are primary factors affecting prognosis[28].

The etiology of EHBD cancers is not well defined[29,30]. A link between gallstones, gallbladder disease and bile duct cancers has been observed[29]. In addition, biliary enteric anastomosis, inflammatory bowel disease, choledocal cysts, and smoking have also been shown to increase the risk of bile duct cancers in both men and women. Other factors such as unsaturated fat intake, body weight, and alcohol show only a weak correlation[30]. Associations between cancer of the bile duct and ulcerative colitis (UC) have been observed[35]. A study by Akwari *et al*[35] reviewed thirteen patients at the Mayo Clinic between 1935-1973 with documented association of UC and bile duct cancer. Onset of bile duct cancer was insidious in each case. Common presentation for these patients was fatigue, anorexia, and weight loss followed by dark urine, pruritus, jaundice and acholic stools[35]. The incidence of bile duct cancer in patients with UC been reported as between 0.4% -1.4%[35]. At onset of cancer, most patients had mild to moderate periodic exacerbations of UC with one having no symptoms[35].

## Presentation and Diagnosis

Patients typically present with painless jaundice and weight loss. Clinically these patients present with scleral icterus, jaundice, dark, tea-coloured urine, and clay-coloured stools. As ductal obstruction worsens patients develop pruritus, hepatomegaly and are at risk for developing ascending cholangitis. If the tumor is confined to right or left branches and occluding the lumen, jaundice may not be present, delaying symptoms and presentation longer[5,31]. Early diagnosis is crucial to survival[13]. Initial investigations after a complete history and physical examination include appropriate blood work which should include liver function tests.

Once a pattern of obstructive jaundice has been identified, abdominal ultrasound is the most effective initial radiologic investigation. Ultrasound will demonstrate a dilated intrahepatic biliary tree and, depending on where the primary tumour is located, dilation of the extrahepatic bile ducts to the level of the tumour. At this stage, the differential diagnosis may include: choledocholithiasis, benign bile duct strictures, sclerosing cholangitis, and pancreatic neoplasms. Imaging of the EHBD can be achieved by perfoming either endoscopic retrograde cholangiopancreatography (ERCP) or by percutaneous transhepatic cholangiography (PTC). At the time of ERCP or PTC, the obstructed bile duct can be stented or drained to allow for decompression of the obstructed biliary system. A subsequent CT scan should be done to help stage the tumour (rule out distant metastases, and evaluate the extent of local invasion). In some centres, hepatic arterial angiography is used to assess local vascular invasion which may preclude surgical intervention. If the EHBD cancer is not resectable, palliation can be obtained with a PTC drain or an ERCP placed drainage stent.[32-34]

**ABOUT THE AUTHORS**

*Ajay Sahajpal is a third-year medical student at the University of Western Ontario. He did his undergraduate degree in biology at the University of Prince Edward Island. Dr. Ward Davies is a hepatobiliary and general surgeon at UWO.*

**Management**

The mean survival for patients for untreated EHBD cancers is 3-6 months[8,36]. Chemotherapy alone has had little role in the treatment of EHBD tumours for curative or palliative management1. These tumours unfortunately do not respond to any great degree to currently available chemotherapeutic agents. Radiotherapy can increase length of survival, quality of life, and shows benefit in patients with previous curative or palliative surgery 1. It may also benefit patients with local recurrences 1. The use of high dose radiotherapy is a feasible therapeutic option for the management of EHBD cancer. Radiation therapy can be delivered by external beam or intracavitary radiotherapy via a PTC drain[37,51].

Indications for use of radiation treatment include: (1) adjuvant therapy following complete resection; (2) palliative radiotherapy for patients with positive margins or local recurrence following surgery; and (3) palliative treatment of nonresectable advanced tumours[1]. Neoadjuvant chemoradiation for EHBD cancers can be used preoperatively[36,38]. Proponents of this approach believe some tumours may be decreased in size to allow for resection and theorize that the neoadjuvant approach may improve survival. Few data exist to support this approach at present.

The side effects of radiation treatment for EHBD cancers are variable and most complaints are related to irradiation of intestinal epithelium[1]. Diarrhea, nausea and vomiting are common1.

The principles of surgical management of EHBD cancers involves complete en bloc resection of the primary tumour with histologically proven negative margins[8,50]. Management based on anatomical location is as follows: (1) upper 1/3 (Klatskin tumour), resection of bifurcation of bile duct +/- associated hepatic resection; (2) middle 1/3, may be amenable to local resection or pancreaticoduodenectomy (Whipple procedure); (3) distal 1/3 of biled duct, pancreaticoduodenectomy. The aim of surgical palliation is to relieve biliary obstruction, thereby decompressing the biliary tree[39]. This is accomplished by performing a biliary enteric bypass.

Surgically placed U-tubes have been used in the past to palliate patients, but are used much less frequently than PTC drains or ERCP-placed stents[3,39]. Percutaneous techniques have associated problems. Mortality may reach up to 25-31% and infection is also a concern[39-41]. External catheters lead to the loss of fluid and electrolytes as well as bile constituents[3]. They also provide a portal of entry for bacteria leading to cholangitis, septicaemia, and liver abscesses[3]. Catheters require daily care, dressing and irrigation. If obstructed they can be changed with ease and may be used as a portal for intracavitary radiotherapy[3]. Mortality rates for percutaneous and endoscopic palliative procedures have been estimated at 15-33% for 30 days post procedure[6,22-23, 42]. This is similar to the perioperative mortality rate for surgical palliative bypass.

Palliative surgical decompression of biliary obstruction in patients with unresectable EHBD cancer involve Roux-en-Y biliary-enteric anastomoses. The location of the bypass depends upon the origin of the primary tumour. The bypass can be performed both intra- and extra-hepatically. The intra-hepatic approach commonly employed is the "round ligament" approach (segment III approach) to the ducts of the left lobe lateral to the ligamentum teres[39].

Guidelines for the choice of a decompression procedure include: (1) general condition or health of the patient; (2) effectiveness of the procedure with respect to quality/duration of survival; (3) associated complications[17]. Regardless of the procedure employed, the goal of palliation is the relief of symptoms of obstruction - jaundice, pruritus, malaise, etc[17].

Surgical resection can be accomplished with acceptable operative mortality and morbidity with respect to length and quality of life[6,12-17]. The key to successful surgical management of EHBD cancers is early and accurate preoperative diagnosis[13]. Invasion of the hepatic artery, portal vein and distal metastases are the usual reasons making these tumous nonresectable at diagnosis[3,13,17,31,38,39]. Contraindications to resection include: (1) regional/distant metastases; (2) bilateral intrahepatic spread beyond second order ducts; (3) invasion of the main trunk of the hepatic artery; (4) invasion of the main trunk of the portal vein[9,13,17,43, 44,45].

A tumour is considered resectable if it is localized to the bile duct. Procedures for radical surgery are individualized and preoperative mapping with PTC and ERCP are crucial to planning. If resection is performed a margin of 1.5 cm from the edge of the tumour especially on the hepatic side is recommended[46].

Postoperative complications include anastomotic leaks, wound infection, bleeding, intra-abdominal abscess formation, sepsis, pancreatitis, and portal vein thrombosis[13]. As a result of improved surgical technique and postoperative management of patients, the postoperative mortality rate has decreased. The perioperative mortality rate depends upon the extent of the surgical resection, but ranges from 2-5%[47].

Liver transplantation as a form of management is not an effective treatment for the management of EHBD cancer. It has been estimated that up to 80% of transplant patients died or manifest disease recurrence within one year[6,24-27]. In the literature, there have been a few reports of curative surgery with liver transplantation for hilar carciomas with adequate long-term survival, if margins are clear and lymph nodes are negative[48,49]. At present, this is still not an accepted therapeutic option and is considered experimental.

**Conclusion**

Extrahepatic bile duct cancers are rare neoplasms with overall five year survival rates less than 5%. En bloc surgical resection with negative histologic margins offers the only chance for cure. Even with surgical resection, 70-75% of patients develop tumour recurrence and ultimately die from the disease. Nonresectable patients can be treated palliatively with PTC drainage of the obstructed bile ducts or via ERCP placed stents. Adjuvant radiotherapy via external beam or intracavitary radiotherapy may improve survival. Palliative radiotherapy may slow progression of the tumour and minimize associated symptoms. Although extra-hepatic bile duct carcinomas are rare, they should be

considered in the differential diagnosis of patients who present with obstructive jaundice.

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# CURRENT OPTIONS IN LOCAL BREAST CANCER TREATMENT

By Helen Lewandowski

## INTRODUCTION

Breast cancer is the most common malignancy in women[1], and the mortality from this disease is second only to that of lung cancer as a cause of death among women[2]. In the general population, an individual woman's lifetime risk for developing breast cancer is one in nine[1]. These numbers are staggering to many women, for whom breast cancer often carries powerful emotional connotations aside from its medical consequences. This disease is particularly frightening because it runs an insidious course. The preclinical, prediagnosis stage of a breast tumour's history and the clinical phases after initial treatment are often measured in decades[3]. Breast cancer has an essentially fixed rate of recurrence for 15-20 years after initial treatment. This is in marked contrast to most other cancers, for which a 5-year survival can be considered a cure[4].

Patients diagnosed with breast cancer and their clinicians are faced with multiple treatment decisions[5]. These include combinations of surgery, chemotherapy, radiation therapy and hormonal therapy. The choice of treatment decisions in breast cancer is largely guided by tumour stage at the time of diagnosis, and patient preference. Breast tumours are staged according to tumour size, presence of nodes or distant metastases, and whether the tumour is inflammatory or ulcerates the skin (see Table 1). In patients with less advanced disease, surgery is still the mainstay of treatment. However, surgery in patients with advanced systemic disease is limited. Radiotherapy and hormonal manipulation are of considerable importance to treat or palliate sites of metastases[1]. This article focuses on current issues in the local treatment of breast cancer, and how it should be timed in relation to systemic treatments.

TABLE 1- Staging and Prognosis of Breast Cancer[6]

| Stage | Description | 5-year survival |
|---|---|---|
| stage 0 | in situ carcinoma | 95% |
| stage 1 | primary tumour <2cm, negative axillary lymph nodes, no distant mtastases | 85% |
| stage 2A | primary tumour <2cm and positive axillary lymph nodes, or primary tumour 2-5cm with negative nodes | 75% |
| stage 2B | tumour 2-5cm and positive nodes, or tumour >5cm and negative nodes | 65%<br>50% |
| stage 3A | tumour >5cm with ipsilateral axillary nodes or fixed lymph nodes | |
| stage 3B | internal mammary lymph nodes, or tumour extending to chest wall and ulcerating the skin | 41% |
| stage 4 | distant metastases | 10% |

## LOCAL TREATMENT OF BREAST CANCER

Historically, the evolution of local treatment has mirrored the prevailing theories on the spread of breast cancer. At the turn of the century, Halsted popularized the radical mastectomy, which involves en bloc resection of the breast, overlying skin, underlying pectoral muscles and axillary contents[6]. This was based on the belief that tumour spread occurs in an orderly fashion by direct invasion and through lymphatic channels. The goal of breast cancer surgery was to remove the maximum amount of breast tissue and axillary lymph nodes in order to fully eradicate the tumour. This policy remained unquestioned dogma for several decades until patient survival analysis in the 1950's and 1960's demonstrated that this radical surgery was not improving patient survival[5]. The realization that failure after surgery was more often due to systemic dissemination of tumour before surgery than to inadequate local surgery caused a shift towards more conservative approaches[5].

Currently, there are several surgical options available to patients with operable tumour. In patients with ductal carcinoma in situ, these include simple mastectomy and breast-conserving surgery (BCS) without axillary node dissection. Patients with invasive stage 1 and 2 cancer have a choice between BCS with axillary lymph node dissection, and modified radical mastectomy (MRM). Simple mastectomy involves a resection extending from the clavicle to the costal margin and from the midline to the latissimus dorsi. The entire axillary tail and the pectoral fascia are completely removed. The skin is excised and skin flaps are similar in thickness to those in a radical mastectomy. However, the axilla is not invaded and axillary nodes are not removed. Modified radical mastectomy consists of removing the breast, nipple-areolar complex and dissection of axillary lymph nodes. In contrast to radical mastectomy, the pectoralis major muscle is spared. Rarely, the pectoralis minor muscle may be removed to facilitate dissection of the higher level lymph nodes. Breast-conserving surgery for invasive cancer includes lumpectomy and quadrantectomy, and consists of resection limited to removal of the breast tumour with a margin of normal breast tissue. Axillary dissection is performed and the patient receives post-operative adjuvant breast irradiation. All these procedures can be performed on an outpatient basis with few complications, few readmissions, and good patient acceptance[7]. Issues which patients and their clinicians must address include the choice of mastectomy versus BCS, the role of axillary dissection, and the timing of chemotherapy relative to surgery.

## MASTECTOMY VERSUS BREAST-CONSERVING SURGERY

Initial treatment for women with stage 1 or 2 breast cancer is surgery. The options available are modified radical mastectomy and breast-conserving surgery. Evidence from six prospective randomized controlled trials has shown that removal of the tumour followed by radiotherapy results in similar survival as mastectomy[8]. Without particular reasons for selecting mastectomy, the choice between BCS and MRM is made according to patient preference. The goal of BCS is to provide satisfactory cosmetic results without compromising local tumour control or survival compared to MRM[9]. However, there are conditions in which mastectomy is favored. It is indicated for diffuse-appearing microcalcifications on mammography, multiple tumours in different breast quadrants, failure to obtain tumour-free margins, and if radiotherapy is contraindicated. Contraindications to radiotherapy include physical disabilities preventing its use, a history of therapeutic irradiation of the breast or chest, treatment during the first or second trimester of pregnancy, scleroderma and SLE[8]. BCS is also not recommended in the presence of a large tumour/breast size ratio or a large breast size[5]. In addition, there are risk factors for local recurrence following BCS. These include extensive ductal carcinoma in situ, young age, multiple tumours and high nuclear grade of tumour. Local recurrence may lead to high patient anxiety and may require salvage mastectomy[9]. In these patients, the risks and benefits of mastectomy versus BCS should be carefully weighed on an individual basis.

In addition, the option of breast reconstruction after mastectomy should be discussed with the patient before any definitive surgery. Breast reconstruction techniques include silicone gel implantation beneath the pectoralis major muscle, and the use of myocutaneous flaps to transfer skin, fat and muscle from distinct parts of the body. Currently, the most commonly used flaps are the latissimus dorsi and transverse rectus abdominis (TRAM) myocutaneous flaps[3]. Regardless of the technique used, the goal of breast reconstruction is re-creation of the breast mound. The main indication for this procedure is the patient's desire to have it performed. The only true contraindications to breast reconstruction are significant comorbid conditions that would interfere with the patient's ability to tolerate a longer operative procedure in the case of immediate reconstruction, or additional procedures in the case of delayed reconstruction[3].

## AXILLARY DISSECTION

The appropriate treatment for the axilla remains controversial. Although Halsted's principles promoted extensive axillary dissection, more recent evidence has questioned the impact of axillary dissection on survival. A trial by the National Surgical Adjuvant Breast Project showed that radical axillary dissection did not positively affect survival in patients with stages 1 and 2 breast cancer[10]. Axillary dissection is also associated with significant surgical morbidity. Possible complications include post-operative infection, paresthesias, alterations in shoulder mobility and lymphedema. However, the presence or absence of metastatic involvement of the axillary lymph nodes is the strongest prognostic factor for patients with primary invasive breast cancer. In addition, extensive axillary dissection is associated with greater reduction of recurrence risk in the axilla than sampling only a few nodes[11]. Thus, the decision on whether to remove axillary nodes and how extensively to do so requires balancing expected health benefits versus side effects.

Currently, there exist clinical guidelines for axillary dissection[11]. These are that removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early invasive breast cancer. For accurate staging and to reduce the risk of recurrence in the axilla, level 1 and level 2 nodes should be removed. Level 1 nodes are those situated lateral to or below the lateral border of the pectoralis minor muscle. These nodes receive most of the lymphatic drainage from the breast. Level 2 nodes are situated deep to the pectoralis minor muscle and receive lymph from level 1 nodes and and also some drainage directly from the breast.

After axillary dissection, irradiation of the axilla should be carried out with caution. Omission of axillary dissection may be considered when the risk of axillary metastases is very low or when knowledge of nodal status will have no influence on therapy. Recently, attention has been focused on the technique of sentinel lymphadenectomy to identify node positive patients[5]. These involve the use of markers such as vital blue dye and technetium-labelled sulfur colloid to identify a sentinel node that drains lymph from the tumour area. If the sentinel node has no evidence of metastatic breast cancer, complete axillary dissection can be avoided. If the node is positive for metastases, axillary dissection should be performed. In a study of 62 patients, the sentinel node was identified successfully in 92% of cases and was positive in all patients found to have metastatic disease. There were no skip metastases[11]. As this technique is refined, a significant amount of axillary dissection and surgical morbidity may be avoided in the future.

## TIMING OF SURGERY AND CHEMOTHERAPY

Traditionally, chemotherapy has been used as an adjuvant therapy following surgical resection in breast cancer. However, neoadjuvant or preoperative chemotherapy has been commonly used in treating various cancers, including breast cancer[12]. The rationale underlying this is that treating metastases at the earliest possible time may avoid rapid growth of metastases after treatment of the primary site and may prevent emergence of resistant clones. Decreasing the size of the primary tumour may make unresectable tumours resectable, may make organ preservation more likely and may improve local control[12]. This approach is mainly used in women diagnosed with stage 3 breast cancer. This includes patients diagnosed with stage 3A disease, which is generally considered operable, and stage 3B disease which is inoperable. Patients with inflammatory breast cancer are also included in stage 3B disease. This subgroup of patients has a particularly poor prognosis, and is characterized by tumours with a rapid onset of erythema,

edema and ridging[13].

Women with stage 3 breast cancer are a complex group in terms of treatment. Currently, multidisciplinary therapy is the treatment of choice for these patients. The accepted strategy is primary or neoadjuvant chemotherapy followed by either surgery, radiotherapy or both. Most patients achieve a response to chemotherapy that results in downstaging of the tumour. With the multidisciplinary approach, 5-year survival rates are 30-60%, compared to 10-20% for local therapy alone[13]. In one study, patients with stage 3 breast cancer including inflammatory disease were treated with chemotherapy followed by surgery and additional chemotherapy. Patients with inflammatory breast cancer or supraclavicular nodes also received adjuvant radiotherapy. Overall 5-year survival was 56%, and was affected by stage (3A or 3B), presence of inflammatory breast cancer and the number of positive nodes[12]. However, it is not clear that the apparent improvement in outcomes resulted from the use of neoadjuvant chemotherapy as much as the use of chemotherapy itself. In another report, the addition of chemotherapy after radiotherapy and surgery in patients with stage 3 breast cancer improved 3-year survival from 57% to 90%, and this difference remained highly significant at 5 years[12].

Therefore, neoadjuvant chemotherapy has not been shown to improve survival when compared to adjuvant chemotherapy for stage 3 breast cancer. However, the use of neoadjuvant chemotherapy may decrease the tumour size and thereby reduce the scope and difficulty of surgery. In one study, patients with locally advanced breast cancer deemed unresectable with primary wound closure underwent 8 weeks of infusional 5-fluorouracil and radiation therapy. 73% of patients had an objective clinical response and all were able to undergo MRM with primary wound closure[14]. Additionally, the use of neoadjuvant chemotherapy reduces the likelihood that skin grafts or complex reconstruction will be required, and may decrease the intensity and morbidity of irradiation needed to treat the breast or chest wall[12].

The use of neoadjuvant chemotherapy in stage 3 breast cancer gave rise to the idea of applying this approach to patients with earlier stage, operable breast cancer. This was based on studies showing "micrometastases" in the blood and bone marrow of a significant number of patients undergoing surgery for early stage breast cancer[15]. It was felt that if these are treated earlier, there is the potential for higher cure rates. However, the use of neoadjuvant chemotherapy for patients with operable breast cancer is controversial. It may achieve significant tumour regression but the primary goal of improving survival has not yet been clearly demonstrated[15]. At this stage, neoadjuvant chemotherapy for operable breast cancer is still considered investigational.

## CONCLUSION

The current management of breast cancer requires a multidisciplinary approach involving surgical, medical and radiation oncologists. This field is constantly evolving. Local and systemic treatment modalities constitute essential aspects of treatment. Several surgical options are available to patients and their clinicians. The choice between mastectomy and BCS should be based on tumour factors and and patient preference following a thourough discussion of these options. Following surgical treatment, the need for adjuvant chemotherapy and/or radiation therapy must be determined based on tumour characteristics such as stage, grade, hormonal status and patient characteristics such as menopausal status and previous medical history. By weighing these factors carefully, breast cancer treatment may be optimized for patients on an individual basis.

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# RECENT ADVANCES IN UNDERSTANDING MELANOMA

By Benjamin Barankin and Lyn Guenther MD

Reducing melanoma mortality is an important public health goal for dermatology, and as a result, has been intensively studied from an epidemiological point of view.[1] The recent literature on melanoma will be discussed.

Melanoma is a malignant disease arising from melanocytes. Melanocytes produce melanin, which generates a brown skin color. Skin cancer is the most commonly diagnosed cancer in the United States and Canada (more than 63,000 Canadians will develop skin cancer each year); anyone born today has a 1 in 7 risk of developing skin cancer during his/her lifetime.[17] Although the incidence of melanoma is lower than other types of skin cancer, it is the most serious form of skin cancer and has the highest death rate.[3] In 1996 in the U.S.A, there were an estimated one million cases of skin cancer; 5 percent of those were melanoma and caused 75% of skin-cancer deaths.[3] In 1999, a 6% increase in melanoma incidence is expected which will mean that 44,200 Americans will be diagnosed this year (3200 in Canada), with approximately 7,300 deaths attributed to melanoma.[3] In Ontario, there are approximately 1400 people diagnosed with melanoma (men > women) each year with approximately 300 deaths per year.[16] A disturbing trend is that the incidence of melanoma in Canada has doubled during the past 20 years.[17] Clearly, more needs to be done in terms of education and prevention. According to Dr. Jason Rivers from the University of British Columbia, the increase in the age-specific incidence for melanoma has stabilized for women, especially for more recent birth cohorts, but in men the rate is still increasing.[26] Table 1 provides skin cancer statistics and trends in Canada.

Melanoma occurs among all racial and ethnic groups. It is more frequent in residents of areas of high ambient solar irradiance, more frequent in sun sensitive people and occurs with highest density on body sites exposed to the sun. In addition, melanoma has been shown to be more frequent in people with intermittent high sun exposure.[2] The useful acronym for identifying a possible melanoma is described in Table 2. The incidence among dark skinned ethnic groups is 1 per 100,000 per year or less, but among light-skinned people has been measured as high as 50 per 100,000.[1] In common with most cancers, melanoma incidence increases with age. However, in Caucasians, it is relatively more common in young adults than most other cancers. In fact, in the U.S.A, melanoma is more common than any noncutaneous malignancy in the 25 to 29 year age group, and it accounts for more years of life lost per case among adults than any major site other than testicular cancer.[3] As well, a gender difference in melanoma location exists; that is, women have an excess of melanoma on the legs, and men have an excess of melanoma on their ears, scalp and especially the posterior trunk.[1,15] In 1996, a study in the Journal of Cutaneous Medicine and Surgery found that men and women had a similar anatomic distribution of painful sunburns, and since the anatomic distribution of melanomas differs, "it would appear that factors in addition to sunburns in adults account for the differences in the anatomic distributions of melanomas in men and women."[15]

**Canadian Skin Cancer Statistics & Trends**

- Half of all new cancers are skin cancers
- Approximately 63,000 new cases of skin cancer will be diagnosed this year in Canada
- Approximately 3,200 new cases of melanoma will be diagnosed this year in Canada
- In 1998, 740 deaths were attributed to malignant melanoma
- The incidence of melanoma doubled among the white population between 1973 and 1991

*Table 1: Skin Cancer in Canadians*[18]

### Unawareness of Melanoma

A high proportion of U.S. residents are unaware of the dangers of melanoma. Forty-two percent of those surveyed had no knowledge of the disease, with the level of awareness lowest among people ages 18 to 24 years.

The survey also found the level of melanoma awareness to be directly related to levels of education and income. Of those with annual incomes of less than $20,000, 60 percent reported they did not recognize the term

**The ABCD's of Melanoma**

***A***symmetry—one half doesn't match the other half.
***B***order irregularity—edges are ragged, notched or blurred (not well circumscribed).
***C***olor—color is not uniform. Shades of tan, brown and black are present; red, white or blue may also be present.
***D***iameter—more than six millimeters.

*Other Warning Signs of Melanoma:*

- change in the size, shape, or color of a mole
- oozing or bleeding from a mole
- a mole that feels itchy, hard, or tender to the touch

*Table 2: Principles in detecting skin cancer*[3]
*Source: American Academy of Dermatology*

**ABOUT THE AUTHORS**

*Ben Barankin is presently a third-year medical student at UWO. Before medical school, he studied life sciences & psychology, completing a psychology degree at Queen's University. Dr. Lyn Guenther is professor and chair of the division of dermatology at the University of Western Ontario.*

melanoma. Only 31 percent of those with annual incomes of $75,000 or more reported no knowledge of the disease.3 It is likely that many Canadians would be similarly unaware of melanoma.

**UV and Melanoma**

The two types of ultraviolet radiation that reach the earth from the sun are ultraviolet A (UVA) and ultraviolet B (UVB). UVB has long been associated with sunburn, while UVA has been recognized as a deeper penetrating radiation. Scientists have long suggested that there may be an association between UVA radiation and malignant melanoma.[3] The wavelength of tanning parlors is UVA. Both tanning parlors[22,23,24] and PUVA (Psoralen & UVA rays) 25 increase the risk of melanoma. It is only recently that UVB rays have achieved similar status in causing melanoma. In the recent study in the May 1998 issue of the American Journal of Pathology, 158 human newborn foreskin grafts on immunodeficient mice were treated with a chemical accelerant 7,12-dimethyl[a]benzanthracene (DMBA) alone or UVB alone, or UVB combined with DMBA, or nothing. The grafts had had no prior sun exposure. Twenty-three percent of the grafts treated with only UVB, and 38% of grafts treated with the combination of DMBA and UVB, developed abnormal pigmented lesions including one human malignant melanoma within 5-10 months of exposure. Untreated human skin xenografts were unchanged, and those receiving only DMBA had very minor changes in a few grafts.

**Sun Awareness**

Efforts to educate people about sun protection have resulted in an increased awareness that sun exposure is dangerous. In a study released in 1997 by the American Academy of Dermatology, a decline in the attitude that having a tan was healthy and an increase in the reported use of sunscreen by adults (35% in 1986 to 53% in 1996) was noted.[3] Unfortunately, during the same decade, the UV exposure of adults, as measured by sunburning (30% in 1986 to 36% in 1996) also increased, as did the regular use of tanning beds (2% in 1986 to 6% in 1996).[3] The risk factors for developing skin cancer are listed in Table 3.

**Sunscreens Increase Cancer?**

- blond or red hair
- blue eyes
- Caucasian
- changed/changing mole
- congenital mole
- fair complexion
- freckles
- immunosupression
- inability to tan
- melanoma in first-degree relative
- one or more large or irregularly pigmented lesions
- personal history of melanoma
- severe sunburns in childhood

*Table 3: Risk factors for skin cancer[4]*
*Source: Centers for Disease Control*

Recent controversy over the role of sunscreens in preventing melanoma has raised questions about the use of these agents. There is concern among some dermatologists that sunscreens alone do not protect against melanoma. Sunscreens might unfortunately lull you into a false sense of security, making you feel that you can stay out much longer than you should. Unfortunately, some individuals with the belief that sunscreen provides sufficient protection, may ignore other sun safety behaviors that could provide additional protection. Subsequently, these same individuals may ignore suspicious marks or lesions as potentially dangerous because they feel that sunscreen alone provides all the protection they need.[3] Historically, the sunscreens used in the past offered poor longer wavelength UVA protection which may have also played a role in melanoma rates not falling with increased sunscreen use. Use of these sunscreens may have increased the long UVA exposure if sun exposure increased since the suncreen decreased burning. There is actually little evidence that protection against the sun protects against melanoma, but this issue is difficult to study epidemiologically.[2] Clearly more research into this matter is necessary.

**Self-Examination**

According to a study published in the May, 1998 *Journal of the American Academy of Dermatology*, people are more motivated to examine their skin for skin cancer if they have had discussions with doctors and if they think they are at high risk for developing melanomas and other skin cancers.[7] It is estimated that skin self-examination (SSE) may reduce mortality from melanoma by 63%. Eighty-one percent of those surveyed who talked to a health care worker were doing SSE compared to 35% who were practicing SSE but had not talked about sunning with a doctor or nurse. SSE was reportedly performed 1.5 times more often by women than men, with white persons performing SSE 1.7 times more often than other races. Some education beyond high school also increased the practice of regular SSE. Thus, there is clear evidence for the need for prevention through skin self-examination in melanoma. This will both ease its economic burden, and more importantly save lives.

**Relating Melanoma Risk to Nevi**

Recent research has found that the risk for melanoma was strongly related to the number of small nevi, large non-dysplastic nevi, and clinically dysplastic nevi. In the absence of dysplastic nevi, increased numbers of small nevi were associated with an approximately 2-fold increased risk, and increased numbers of both small and large non-dysplastic nevi were associated with a 4-fold increased risk. One clinically dysplastic nevus was associated with a 2-fold increased risk, while 10 or more conferred a 12-fold increased risk. As well, there is an estimated 81.6%[21] to 100%[19] lifetime risk of melanoma in a person with familial dysplastic nevi who has two relatives with melanoma.[19] In regards to congenital nevi, they appear to significantly increase the risk of malignant melanoma if they are large (= 20cm).[3,20] The reported risk in patients with large congenital nevi varies from 3.8% - 18%.[20]

**Genetic Testing for Melanoma?**

It has been shown that approximately 8 to 12% of melanomas appear to be inherited in an autosomal dominant fashion. A French study published in the October 1995 issue of the Archives of Dermatology concluded "a familial investigation should be performed for each patient with cutaneous malignant melanoma (CMM), particularly when he or she exhibits phenotypic risk factors for CMM such as red hair and atypical moles."[13]

Furthermore, there is now strong evidence that germline mutation of the CDKN2A gene on chromosome 9p21 predisposes to melanoma in a subset of melanoma-prone families. A study published recently in the Journal of Cutaneous Medicine and Surgery concluded "the identification and subsequent surveillance of unaffected individuals who have a genetic predisposition to melanoma may lead to the detection of early (curable) melanomas and to a reduction in mortality."[10]

**Cost of Treating Melanoma**

A recent study in the U.S. found that the annual direct cost of treating newly diagnosed melanoma in 1997 was estimated to be $563 million. Dr. Jason Rivers from the University of British Columbia noted that the Canadian figure is unknown, but estimated it to be 5-10% of the American cost.[26] The American study broke down the cost of treating each stage of the disease and found that Stage I and II disease each comprised about 5% of the total cost; stage III and stage IV disease consumed 34% and 55% of the total cost, respectively. About 90% of the total annual direct cost of treating melanoma in 1997 was attributable to less than 20% of patients (those patients with advanced disease, that is, stage III and stage IV). The study concluded that "in addition to the potential survival advantages, aggressive primary prevention through sun protection and intensive screening to enhance earlier detection should reduce the economic burden of melanoma care."[5]

**Laboratory Tests And Imaging for Melanoma**

There is an ongoing controversy about the use of laboratory and imaging studies for baseline and for follow-up evaluations to detect malignant melanoma (MM) metastases. Some argue that no laboratory tests or imaging studies should be routinely ordered for patients who exhibit no evidence of metastases on history or physical examination. However, CXR screening may be suggested since it detects about 5% of metastases which would have been classified clinically as AJCC (the American Joint Committee on Cancer) stage I or II MM. LDH levels, which are inexpensive, are routinely ordered by some physicians because metastases have been infrequently detected in asymptomatic patients. Some physicians also consider computed tomography (CT) scans for patients who have thicker primary MM; CT of the chest should be considered especially if the patient has cervical or axillary adenopathy.[12] The final position from the Guidelines for the Management of Cutaneous Melanoma is that "extensive investigation for systemic metastases in patients with primary melanoma is not recommended" and that "investigations such as CT, magnetic resonance imaging (MRI) scans, and positron emission tomography (PET) scans should be utilised only where specific symptoms suggest the presence of metastases.[9]

**Advances in Melanoma Therapy**

The improvement of treatment options and survival rates for melanoma patients is an important health care concern as melanoma is the tenth most common type of cancer in Canada.[18]

Several advances in the evaluation of regional lymph nodes, adjuvant therapy and genetic immunotherapy for the treatment of malignant melanoma have improved the treatment options for patients, as well as the five year survival rate for many patients according to a study in the May 1998 issue of the *Journal of the American Academy of Dermatology*.[8]

The evaluation of regional lymph nodes has proved to be an important predictor of the long-term outcome. In patients with nodal metastases, the actual number of diseased nodes is the most important factor for the prognosis and overall survival. Selective node dissection (which focuses on the main, or sentinel, node) may be used to determine the condition of the entire group of nodes.[9] Another evaluation of the regional lymph nodes, intraoperative radiolymphatic mapping, increases sentinel node identification to 99 percent.[8] Both of these options are still controversial, and confirmation is needed.

The most significant prognostic factor for melanoma is disease stage at presentation. While AJCC stage I and II melanomas (localised disease) have five year survival rates of ≥ 85%, the rate for stage IV (metastatic) disease is less than 5%, with median survival time of 6-10 months.[11] Because of the poor prognosis of stage IV disease, clinical trials of adjuvant therapy are underway. A promising but controversial adjuvant therapy involves interferon alpha 2b which may improve the long-term survival rates of patients.[8] A study published in the January 1996 issue of the Journal of Clinical Oncology showed that "IFN alpha 2b was the first agent to show a significant benefit in relapse-free and overall survival of high-risk melanoma patients in a randomized controlled trial."[14] However, at a recent conference addressing the issue, it was noted that only high dose interferon therapy (as opposed to low dose) may have potential benefit, but that at present, since clearly more research is needed, there is no standard therapy for high-risk melanoma patients.[11]

Genetic immunotherapy focuses on applications of gene therapy as it applies to immunotherapy based upon the understanding that melanoma appears to be an immunoresponsive disease. One approach to gene therapy involves genetically modifying tumor cells to make them more immunogenic. Another approach involves the injection of foreign genes directly into the tumor in an attempt to impact the immune response to the tumor.[8]

Due to the inconclusive evidence that adjuvant therapy is beneficial for persons with melanoma, the Guidelines for the Management of Cutaneous Melanoma recommend referral to a melanoma centre for adjuvant therapy such as immunotherapy, chemotherapy or gene

therapy in patients with melanomas > 4mm in thickness and/or with involved nodes, whose prognosis is poor.[9]

Melanoma is certainly one of the most studied conditions in Dermatology, and with reason. With the promising research into its treatment and prevention, we hope to see declines in the incidence and improved survival in the near future.

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# CARDIOVASCULAR MANIFESTATIONS OF RHEUMATOLOGIC DISEASES: A REVIEW

*By Dan Hackam BSc, Editor-in-Chief*

A great variety of systemic diseases and syndromes display cardiovascular manifestations, and among these, the rheumatologic diseases figure prominently. Such effects range from the trivial and the benign, such as most pericardial effusions occurring in the context of collagen vascular diseases, to the severe and life-threatening, eg myocardial fibrosis occurring in scleroderma.[1] This review serves to briefly highlight the cardiac consequences of some of the more common rheumatoid conditions.

Systemic lupus erythematosus (SLE) is a multisystem disorder in which tissues are damaged by autoantibodies and immune complexes[2] The vast majority of cases occur in women in their child-bearing years. The disorder has a prevalence of 20-50 cases per 100,000, and is more frequent in blacks than in whites.

Pericarditis is the most common cardiac manifestation of SLE, and occurs in two thirds of patients. It is generally benign, sometimes associated with pericardial effusions, and rarely leads to tamponade or constrictive pericarditis. If not evident from the clinical background of SLE, the diagnosis can be made by the presence of lupus erythematosus cells or a titre of antinuclear antibodies. Valvular insufficiency is a rare consequence of SLE and is a result of Libman Sachs endocarditis, which may lead to systemic emboli. Myocarditis may result in conduction abnormalities, heart failure, or sudden death.

The antiphospholipid syndrome is a well-known subset of lupus and is associated with valvular dysfunction, a tendency towards thrombosis, myocardial infarction (MI), pulmonary hypertension, and cardiomyopathy. MI occurring in a lupus patient may be due to this prothrombotic tendency, or may be the result of lupus vasculitis, chronic steroid treatment, or coronary atherosclerosis. Anticoagulation is recommended with high dose coumadin treatment, aiming for an INR between 2.5 and 3.0.

Rheumatoid arthritis (RA) is another multisystem disease with diverse multiorgan effects, the *sine qua non* being an inflammatory synovitis that chiefly affects the peripheral joints.[3] The prevalence of this disorder is approximately 0.8%, with a female:male preponderance of 3:1. RA may affect any part of the heart, with pericarditis again being the most common cardiac complication (10-50% of RA patients); it is particularly prevalent in those patients with subcutaneous nodules. Coronary arteritis, occurring in up to 20% of patients (based on autopsy studies), may infrequently result in the occurrence of MI or angina pectoris. Myocarditis and valvular insufficiency are further, rare complications.

Raynaud's phenomenon can be defined as episodic ischemia of the fingers or toes occurring in the context of exposure to cold weather or objects.[4] It may be primary and idiopathic, in which case it is known as Raynaud's disease, or may be secondary to an underlying disease, medication, or other process. Raynaud's disease has a female:male preponderance of 5:1, with a peak onset between the ages of 20 and 40. The disorder is associated with primary pulmonary hypertension and coronary vasospasm (also known as variant angina).

Scleroderma is a multiorgan disease typified by fibrosis of the skin, blood vessels, and viscera.[5] Cardiovascular complications are frequent in the diffuse cutaneous systemic sclerosis subset, and rare in the more limited form of scleroderma. These manifestations include pericarditis, heart failure secondary to hypertension or cor pulmonale, and arrhythmias. Left-sided heart failure occurs in up to 30% of patients with diffuse cutaneous scleroderma.

Ankylosing spondylitis (AS) is an inflammatory disorder that characteristically affects the axial skeleton, starting in the 2nd or 3rd decade of life.[6] The male:female preponderance is 3:1. The two cardiovascular effects of AS are aortic regurgitation and conduction defects. In a small percentage of patients, all three layers of the aortic valve and proximal thoracic aorta are thickened and scarred, resulting in aortic insufficiency. The frequency of both the valvular abnormality and the conduction defects increases with the duration of the disease.

In closing, these cardiovascular manifestations are by no means the commonest effects of rheumatological disorders, but when they occur, they may be devastating to the patient. It is therefore important that the non-cardiologist have a good grasp of these complications, in terms of natural history, diagnosis, and management.

**ABOUT THE AUTHOR**

*Dan Hackam is the editor-in-chief of the University of Western Ontario Medical Journal. He has an interest in academic medicine and cardiology.*

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# PrNORVASC*

(amlodipine besylate)

**Brief Prescribing Information**
NORVASC
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

**ACTION AND CLINICAL PHARMACOLOGY**
NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

**INDICATIONS AND CLINICAL USE**
**Hypertension**
NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.
NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.
**Chronic Stable Angina**
NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

**CONTRAINDICATIONS**
NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

**WARNINGS**
**Increased Angina and/or Myocardial Infarction**
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.
**Outflow Obstruction (Aortic Stenosis)**
NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).
**Use in Patients with Impaired Hepatic Function**
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).
**Beta-blocker Withdrawal**
NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

**PRECAUTIONS**
**Use in Patients with Congestive Heart Failure**
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.
**Hypotension**
NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.
**Peripheral Edema**
Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
**Use in Pregnancy**
Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
**Nursing Mothers**
It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.
**Use in Children**
The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.
**Use in Elderly**
In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).
**Interaction with Grapefruit Juice**
Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.
**Drug Interactions**
As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.
Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.
Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.
Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.
**Cimetidine, Warfarin, Cyclosporin, Digoxin:** Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:
- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

**Antacids**
Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
**Beta-blockers:** When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

**ADVERSE REACTIONS**
NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.
**Hypertension**
In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):
**Cardiovascular:** edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).
**Angina**
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):
**Cardiovascular:** edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
**Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.
Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**
**Symptoms**
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.
**Treatment**
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

**DOSAGE AND ADMINISTRATION**
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.
**Use in the Elderly or in Patients with Impaired Renal Function**
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).
**Use in Patients with Impaired Hepatic Function**
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

**DOSAGE FORMS**
**Availability**
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

**STORAGE**
Store at 15-30°C. Protect from light.

**REFERENCES: ANGINA**

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**REFERENCES: HYPERTENSION**

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# BP CONTROL THAT ENDURES. FROM ONE DAY WELL INTO THE NEXT.

*The Pyramids and Sphinx at Giza*

NORVASC*
(amlodipine besylate)
FOR HYPERTENSION

## Long-acting BP control for mild-to-moderate hypertensives

- effectively controls BP at target levels for a full 24 hours and beyond[1,2†]
- intrinsically long half-life maintains plasma levels to reduce BP up to 24 hours after a missed dose[3,4†]
- shown to be more effective than felodipine at the same dose[5,6¶]

## Impressive tolerability after 4 years

- compared with antihypertensives from four different classes, more NORVASC* patients remained on therapy after 4 years[7‡]
- only 3% withdrawal rate among 12,831 patients in 16 clinical studies[8]

† NORVASC* should always be prescribed as once-daily therapy.
¶ NORVASC* 5-10 mg o.d. (n=103) versus felodipine ER 5-10 mg o.d. (n=103) after 8 weeks (p=0.036) 82% of NORVASC* patients reached target DBP of ≤90 mmHg versus 69% for felodipine.
‡ NORVASC* (n=114), 83% of NORVASC* patients remained on therapy after 48 months.

NORVASC* is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable. The most common adverse reactions include edema (8.9%) and headache (8.3%).[1]

Consult prescribing information for important safety information and drug interactions.

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