Determination of Left Atrial Appendage Morphology

To the Editor:

Veinot et al1 reviewed 500 heart specimens from autopsies during a 22-year period. They described the anatomy of the left atrial appendage (LAA) by determining orifice diameter, width, length, and number of lobes. They found orifice size, width, and length to be age and sex related. In men and women aged >20 years, mean orifice diameters of 1.16 and 1.07 cm, length of 2.59 and 2.53 cm, and width of 1.83 and 1.66 cm were found, respectively, as well as 1 to 4 lobes.

In a study on 220 LAA casts obtained shortly after death,2 we determined LAA morphology by describing the course and ramifications of the principal axis and by measuring minimal and maximal orifice diameters, length (bottom to top), width (at right angles), and volume. The course of the principal axis was straight (7%), slightly bent and slightly spiral (23%), slightly bent and extremely spiral (5%), extremely bent and slightly spiral (24%), or extremely bent and extremely spiral (42%). Fifty-six percent of the casts had >5 branches (orifice area >10 mm²), and 47% had >40 twigs (orifice area 1 to 10 mm²). The mean minimal and maximal orifice diameters were 15 and 21 mm, respectively. Mean length was 30 mm, width was 31 mm, and volume was 5220 mm³. The casts of 35 cases with normal cardiac findings were not different from those that showed pathological cardiac findings at autopsy.

Differences between the results of the study by Veinot et al and our results can be explained as follows:

1. The specimens used in the 2 studies were of different age and type of conservation. It is possible that the years of conservation led to a shrinkage and change of the elastic properties of the LAA tissue, whereas casting possibly led to dilation of the LAA. This assumption is supported by the shorter LAA length in the study by Veinot et al compared with our study. Furthermore, the number of LAA outpouchings is lower in their study compared with our study.

2. Veinot et al measured the LAA tissue, whereas we measured synthetic resin casts.

3. The orifice diameters were measured differently.

4. Veinot et al measured width as the widest external width, whereas we measured at right angles, perpendicular to the bottom-to-top axis.

5. The definition of lobes in the study by Veinot et al differed from our definition of branches and twigs.

We conclude that postmortem casts may reflect the intravitam morphology of the LAA more closely than specimens conserved for years. We demonstrate that the anatomy and morphology of the LAA is more complex, bizarre, and variable than previously thought. This should be considered when images of the LAA are being interpreted, in particular when thrombi are being diagnosed.

Günther Ernst, MD
Claudia Stößberger, MD
K.A. Rudolfstiftung
Josef Finsterer, MD
Neurologisches Krankenhaus Rosenhügel
Wien, Österreich

Correspondence

Letters to the Editor must not exceed 400 words in length and may be subject to editing or abridgment. Letters must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Only some letters will be published. Authors of those selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication.


Response

We have read with interest the comments made by Dr Ernst and colleagues on our article on left atrial appendage (LAA).1

The differences between our results and those of Ernst et al2 have been explained in their letter. We do not agree with the comments that postmortem casts reflect the intravitam morphology of the LAA more closely than specimens conserved for years. Both techniques have their own limitations. It is surprising to note no differences in normal specimens versus those with cardiac pathology, particularly if those with cardiac pathology had mitral valve disease.

The predominant issues that are important from the standpoint of clinicians who perform transesophageal echocardiography are not necessarily the length and the orifice diameter but the presence of lobes and pectinate muscles, given that they can be sources of error in the interpretation of the study.

Ernst et al and our group make similar points that the morphology and anatomy of the LAA are complex and variable and that these facts need to be considered when images are interpreted.

We have documented cases in which thrombi have been present in 1 lobe but not in the other lobes of the LAA. Therefore, interrogation of the LAA needs to be made in multiple imaging planes, and the preferred technology of choice is either a multiplane or at the very least a biplane transesophageal transducer.

Bijoy K. Khandheria, MBBS
Federico Gentile, MD
James B. Seward, MD
A. Jamil Tajik, MD
Division of Cardiovascular Diseases and Internal Medicine
John P. Veinot, MD
Phillip J. Harrity, MD
William D. Edwards, MD
Division of Anatomic Pathology
Kent R. Bailey, PhD
 Mayo Clinic and Mayo Foundation
Rochester, Minn


Regular Physical Activity and Risk Factors for Coronary Heart Disease

To the Editor:

We read with interest the article by Hsieh et al reporting a dose-dependent benefit from small amounts of physical activity on some coronary risk factors in Japan. According to the Seven Countries Study, Japanese people exhibit a very low incidence of coronary heart disease (CHD). Thus Hsieh et al found, in a low-risk population, an effect of regular physical activity on hypertension, abnormal glucose tolerance, hypertriglyceridemia, and low HDL cholesterol levels, but they did not see any effect on total plasma cholesterol. Unfortunately, LDL cholesterol, the most important risk factor for CHD, was not investigated in their study.

To elucidate the effects of exercise on lipoprotein metabolism, we performed a prospective study of aerobic exercise in individuals with high risk for CHD, including elevated LDL cholesterol and apolipoprotein B, the key risk factors of CHD.

In accordance with Hsieh et al, we found a significant benefit from regular physical activity on triglycerides (196.15 versus 148.84 mg/dL in sedentary and physically active individuals, respectively; P < 0.001) and on HDL cholesterol (52.15 versus 55.14 mg/dL; P < 0.05). Also, compared with no physical activity, regularly performed aerobic exercise was significantly associated with lower LDL cholesterol (154.42 versus 129.41 mg/dL; P < 0.001), lower apolipoprotein B (133.33 versus 109.30 mg/dL; P < 0.001), and higher apolipoprotein A levels (158.37 versus 177.29 mg/dL; P < 0.001). Lipoprotein(a) was significantly lower after exercise but that total cholesterol and LDL cholesterol levels may be at least as effective as lowering LDL cholesterol levels in the prevention of coronary heart disease. It has also been reported that LDL cholesterol levels increase significantly after exercise but that total cholesterol and LDL cholesterol levels do not change significantly.

LDL cholesterol is not on our routine examination list. However, we calculated LDL cholesterol values according to the formula of Friedewald when triglyceride levels were <400 mg/dL. LDL cholesterol levels were 133.4.23.22, 129.7.31.7, 131.4.30.3, and 128.6.28.0 mg/dL (mean ± SD) for the sedentary groups and the groups who exercised 1, 2, and ≥3 days per week, respectively; there was a significant difference among groups (P = 0.0377 by 1-way ANOVA). However, we did not find any difference between the groups by the Tukey-Kramer honestly significant difference test. We think the study of Benzer and colleagues differed from ours in the following ways: (1) their studies comprised both men and women; (2) the body mass index of the sedentary group was a little higher than in the exercise group in their studies (mean, 26 versus 25 kg/m²); and (3) the degree of physical activity might have been higher in their studies.

In any case, the effect of the degree of physical activity on total cholesterol and LDL cholesterol levels requires further exploration.

Shiu Dong Hsieh, MD
Hideyo Yoshinaga, MD
Medical Center of Health Science
Toranomon Hospital
Tokyo, Japan

Takashi Muto, MD
Department of Public Health
Juntendo University
Tokyo, Japan

Yutaka Sakurai, MD
Department of Public Health
National Defense Medical College
Saitama, Japan

Correspondence


Response

According to the Helsinki Heart Study report, elevating HDL cholesterol levels may be at least as effective as lowering LDL cholesterol levels in the prevention of coronary heart disease. It has also been reported that LDL cholesterol levels increase significantly after exercise but that total cholesterol and LDL cholesterol levels do not change significantly.

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In any case, the effect of the degree of physical activity on total cholesterol and LDL cholesterol levels requires further exploration.

Shiu Dong Hsieh, MD
Hideyo Yoshinaga, MD
Medical Center of Health Science
Toranomon Hospital
Tokyo, Japan

Takashi Muto, MD
Department of Public Health
Juntendo University
Tokyo, Japan

Yutaka Sakurai, MD
Department of Public Health
National Defense Medical College
Saitama, Japan

Azithromycin, *Chlamydia pneumoniae*, and Intimal Thickening

*To the Editor:*

In the February 24, 1998, issue of *Circulation*, Muhlestein et al. reported on cholesterol-fed rabbits that had repeated nasal inoculations of *Chlamydia pneumoniae* and whose thoracic aortas showed intimal thickness 3 months later. The authors concluded that weekly treatment with azithromycin for 7 weeks after infectious exposure prevents accelerated intimal thickening. We appreciate the importance of the study and see the implications of its results; however, the conclusion in its present form raises some comments. First, we would be interested in the data on whether and to what extent neointima had been seen at the intermediate time points of weeks 3 and 10. The question remains whether azithromycin treatment really prevents intimal thickening because of its anticlamydia eff. It is important to note that it is uncertain precisely when neointima formation in response to the *C pneumoniae* pathogen starts. After endothelial denudation, neointima is usually seen after 10 to 14 days. Other possibilities related to the authors’ conclusions could be (1) that this antibiotic (similar to the macrolide rapamycin) simply has induced lesional regression or (2) even has acted via both preventive and regressive mechanisms. Furthermore, one would like to see the specific effects of *C pneumoniae* (and possibly those of azithromycin) in the absence of cholesterol feeding.

Second, we would like to comment on the conclusion drawn from the lesional morphology of the aortic section determined as representative of the infected/treated animal group. The original photomicrograph of Figure 2C shows a circumscribed, eccentric intimal lesion with a dense texture, whereas adjacent parts of the vascular wall were free of intimal disease. This lesion contrasted significantly with the large concentric lesion, with its loose texture, found in infected/untreated animals (Figure 2A). If it is true that apoptosis is the key mechanism that determines intimal cell density and mediates intimal lesion regression, as has been suggested recently, one would expect to find a homogeneously reduced, concentric intimal lesion or even to find no lesion. In addition, the presence of a padlike intimal lesion with a smooth surface, as illustrated in Figure 2C, points to a newly developed lesion (after a phase of complete regression). Irregular luminal surface, as illustrated in Figure 2C, points to a newly developed lesion (after a phase of complete regression). In future larger studies, pathological evaluation of neointimal formation at multiple time points during the course of the study should be performed to determine details of the time course of pathophysiological events that occur after chlamydial infection.

Second, regarding azithromycin’s mechanism of action, we agree that we cannot determine from this study the exact mechanism whereby azithromycin exerted its actions. Whether intimal proliferation is affected through its antibacterial effect or by some other mechanism will require further study.

Third, regarding the effect of cholesterol in the diet, this article evaluated chlamydia infection occurring on top of a low-dose-cholesterol–supplemented diet; other studies have documented similar, although less marked, effects on intimal thickening in rabbits receiving standard noncholesterol-enriched chow.

Fourth, regarding the interpretation of pathological findings, Bauriedel et al. allego, on the basis of their work, that if apoptosis is important, the morphological appearance of the plaque in Figure 2C suggests newly developed disease. We do not know whether the sequence of morphology they describe in restenosis is applicable to this model/diet/animal. The number of animals and sections that we reviewed precludes our making general statements about the morphology in this study. That is why we chose to make semiquantitative measurements instead. We concur that additional studies are indicated.

Joseph B. Muhlestein, MD
Jeffrey L. Anderson, MD
Elizabeth H. Hammond, MD
Liping Zhao, BS
Sanjeev Trehan, MD
Eric P. Schwobe, BS
John F. Carlquist, PhD
University of Utah
LDS Hospital
Salt Lake City, Utah


**Acupuncture for Relief of Angina**

*To the Editor:*

I read with interest the ESBY study (Electrical Stimulation versus bypass surgery in severe angina pectoris) by Mannheimer et al. They found that spinal cord stimulation (SCS) has antianginal and anti-ischemic effects in severe angina pectoris and concluded that CABG and SCS are equivalent methods in terms of symptom relief.

In a previous report, these authors showed that myocardial extraction of β-endorphin during control atrial pacing changed to release at the maximum pacing rate during SCS. Furthermore, their results indicate local myocardial turnover of β-endorphin, leukokinin, and calcitonin-gene–related peptide. Han et al. found that electroacupuncture of different frequencies was able to activate different opioid systems in the spinal cord of the rat: low frequency...
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Li et al published this year in and ischemic heart disease of utmost importance, eg, the study by comparable to SCS. SCS is a standardized central nervous system method in this patient group. According to our experiences, acupuncture is an unpractical thus does not deprive patients of a warning signal.4 Furthermore, myocardial ischemia creates anginal pain during stimulation and it has also been shown that several reports from different centers. It has also been shown that myocardial ischemia creates anginal pain during stimulation and effects of spinal cord stimulation on pacing-induced angina pectoris. Cardiology. 1998:89:170–177.


Zhou XQ, Liu JX. Metrological analysis for efficacy of acupuncture on ischemic infarct. 

Tsung O. Cheng, MD Professor of Medicine The George Washington University Washington, DC


Response

We thank Dr Cheng for his interesting comments on our study. Despite some attempts to perform “blind” studies with acupuncture, we are not aware of any satisfactory way to achieve this.1–3 We could not find any method to make a proper blinding in the ESBY study. Our group has tried acupuncture previously in patients with angina pectoris. There are some studies that may indicate an anti-ischemic effect of acupuncture on myocardial ischemia with only partial effect in humans.1–3 In contrast, the effect of SCS on myocardial ischemia is well documented in several reports from different centers. It has also been shown that myocardial ischemia creates anginal pain during stimulation and thus does not deprive patients of a warning signal. Furthermore, according to our experiences, acupuncture is an unpractical method in this patient group.

Acupuncture is an afferent stimulation technique that is not comparable to SCS. SCS is a standardized central nervous system stimulation with well-defined, completely reproducible parameters. However, we find further research in the field of acupuncture and ischemic heart disease of utmost importance, eg, the study by Li et al published this year in Circulation.5

Clas Mannheimer, MD, PhD Tore Eliasson, MD, PhD Henrik Norrsell, MD, PhD Multidisciplinary Pain Centre Department of Medicine Östra Hospital Gothenburg, Sweden


Prodrug ACE Inhibitors

To the Editor:

In a recent issue of Circulation, Brown and Vaughan1 reviewed ACE inhibitors. They stated that captopril and lisinopril are active drugs and listed 7 other ACE inhibitors approved in the United States that are inactive prodrugs until metabolized in the liver. More information should be provided on this clinically important subject.

First, the package inserts say that liver disease may impair activation of prodrugs. This may apply to liver congestion due to heart failure. Second, 7% to 10% of the white population are so-called poor metabolizers, who have impaired activation of prodrugs.2 Percentages for other ethnic groups are unknown, but genetic polymorphism is expected to vary pharmacokinetics.3 Third, the review discusses drug interactions but omits the fact that erythromycin, antidepressants, ketoconazole,4 and even grapefruit juice5 inhibit liver enzymes needed to activate prodrugs.

These facts suggest many of our patients may be taking medication of impaired potency. Clinicians have no access to blood assays for the active metabolites. Data necessary to clarify these issues are not available. Therefore, when hypertension or heart failure fails to respond adequately to a prodrug ACE inhibitor, we should consider a trial of captopril or lisinopril.

Stephen H. Rabinowitz, MD Division of Cardiology North Shore University Hospital at Forest Hills Forest Hills, NY


Response

As Dr Rabinowitz states, and as indicated in our article, the majority of ACE inhibitors are administered as prodrugs, which are then deesterified by the gut and liver. Although liver disease may impair activation of the prodrug, this is not of much therapeutic importance because the dose of drug can be titrated upward, and the parent compound is not toxic. With respect to drug interactions, there are no data suggesting interactions with drugs that affect either CYP2D6 (the P450 cited for which 7% to 10% of whites are poor metabolizers) or CYP3A4 (ketoconazole, erythromycins, and grapefruit juice).

Nancy J. Brown, MD
Division of Clinical Pharmacology
Douglas E. Vaughan, MD
Division of Cardiology
Vanderbilt University
Nashville, Tenn
Regular Physical Activity and Risk Factors for Coronary Heart Disease
Werner Benzer, Robert Bitschnau, Ernst Groechenig, Stefan Aczel and Heinz Drexel

Circulation. 1998;98:2356
doi: 10.1161/01.CIR.98.21.2356

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/98/21/2356

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