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SCREENING AND DIAGNOSIS

Protocol 2

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13. ABSTRACT (Maximum 200 words)

The aim of the study has been to establish the incidence of various etiologies of chest pain in active duty women and to improve the accuracy, efficiency and cost-effectiveness with which we are able to confirm or exclude cardiac disease in women with chest pain and then, if cardiac pathology is eliminated, to expedite the determination and treatment of the true cause. Our stated goal has been to enter 100 women between 18 and 70. This has been hampered by the late release of funding and the inclusion of Fitzsimmons on the base closure list. As of 31 July 95, twenty women have been enrolled in the study. Preliminary data demonstrates a high rate of cardiac catheterization in women enrolled because of the high incidence of inconclusive reporting from nuclear stress testing (cardiolite GXT). There has been a problem with readings indicating artifact and breast attenuation, or shifting breast attenuation making definitive diagnosis difficult and necessitating cardiac catheterization. Enrollment is steady; however, it is unlikely that the stated goal of 100 within one year will be met. It is hoped that a second study site at Walter Reed will facilitate enrollment of additional patients and completion of the study.

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Jennifer L. Calaga
Signature Date 10/14/95

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I. Introduction and Background

This study was proposed to establish the incidence of various etiologies of chest pain in active duty women and to improve the accuracy, efficiency and cost-effectiveness with which we are able to confirm or exclude cardiac disease in women with chest pain and then, if cardiac pathology is eliminated, to expedite the determination and treatment of the true cause. Evaluation of chest pain and "clearance" for physical activity / deployment is a common problem presenting the general army medical staff at the MEDDAC and clinic levels. Active duty women presenting with chest pain represent a unique subset of challenging patients. Sensitivity and specificity of non-invasive cardiac testing for ischemic heart disease are not gender identical. Standard stress testing is poorly predictive in women and often yields false positive results, leading to extensive and costly procedures including cardiac catheterization. Women with cardiovascular disease are also more likely to have atypical presentations or variant angina. Further, women are at higher risk for morbidity and mortality during invasive diagnostic procedures. Readiness/deployment requirements necessitate that military women are more likely to undergo cardiac catheterization than their civilian counterparts. Identifying non-invasive, lower risk diagnostic procedures for identifying coronary artery disease in women could result in decreased risk to female soldiers, lessen loss of time from duty and prevent delay of treatment. This study employs echocardiography, stress echocardiography and myocardial perfusion exercise test with cardiolute to evaluate all patients. The usefulness of echocardiographic stress testing as an alternative to costly nuclear testing and invasive testing can be analyzed and possibly established in women.

Women with chest pain in whom cardiac disease has been excluded are referred next for gastroenterology evaluation. Frequently after life-threatening cardiac conditions are excluded there is still an undetermined cause of the chest pain. A minor structural anomaly, such as mitral valve prolapse may be present, but not clearly established as the cause. This study is also geared to document the incidence of specific etiologies of gastrointestinal pathology in women judged to have non-cardiac pain and success of treatment. Positive results from this evaluation will be correlated with results from the symptomatic and historical questionnaires.

Women with persistent symptoms but no diagnosis after both cardiology and gastroenterology evaluation will then be referred for other evaluation such as pulmonary function testing, stress-psychological/stress evaluation, rheumatology or other discipline in what ever order appears to be most clinically indicated.

II Goal and Realistic Goal Adjustments

The goal of the study has been to enroll 100 consecutive women between the ages of 18 and 70 with a history of chest pain (tightness, pressure etc.) without prior documented cause of chest pain or known coronary artery disease. Enrollment has occurred at a steady pace since the first week of May. Enrollment did not begin until May because of the delay in release of funding, need to hire and orient study personnel, and time required for creation of computer data base and general organization necessary to the initiation of any study. At this time, it is unlikely we will

meet our goal of 100 volunteers at Fitzsimons. Fitzsimons position on the base closure list has impacted the study in many respects. The primary investigator has been transferred to Walter Reed. In addition, nuclear medicine support has diminished. We are now limited to three nuclear study slots per week. Referral to other medical disciplines has become increasingly difficult because of fewer specialists on staff and thus fewer slots for patient appointments. A more realistic goal for total enrollment over the next 6 months would be a total of 50 patients if no further reductions in support occur. Thus, a second site at Walter Reed is being considered and increased funding applied for. This would facilitate increased enrollment and Dr. Calagan, who will be assigned to Walter Reed, can continue to provide study leadership.

III Preliminary Results

Enrollment has been steady and as of 31 July 1995 **twenty** patients have been enrolled in the study. This covers a three month time period as enrollment did not truly begin until May 1995. Fifteen patients have completed the cardiac work-up. The only new patient enrollment exclusion have been patients requiring oxygen with severe pulmonary disease. There was one drop out and we have had difficulty scheduling two patients for the GI portion of the study and they may become drop outs. There has been one adverse event.

Demographics

Twenty women between the ages of 25 and 65 have been enrolled. Ethnic background/race includes 14 white women, 3 black women, 2 asian women and 1 hispanic woman. This is a 30% minority participation rate. Five participants are currently on active duty and 3 are Persian Gulf veterans.

Medical Demographics

Risk Factors (20 Patients)	No. Pts
Positive family history of CV disease	17
Hypertension	8
Smoking	4
Birth Control or Hormone Replacement Therapy	12
Diabetes	2
Cholesterol > 200	10
LDL > 130	4
Hypothyroid on medication or abnormal TSH	8

Echo

Stress Echo results appear to promise better specificity in the diagnosis of coronary artery disease than nuclear tests. Based on cardiac catheterization results, there has been only one false positive stress echo (19 patients have had stress echo). We do not know if this is statistically significant at this time.

Initial Echocardiographic Analysis

Echocardiograms from 16 patients were available for review. For the purposes of this report, only patients without significant ASHA (n=15) were analyzed. These patients were divided into two groups based on the presence or absence of hypertension, since this condition may significantly alter cardiac structure and function. The results of this initial analysis follows. Data are expressed as mean \pm standard deviation. Data did not meet the criteria for parametric statistical analysis; therefore, the groups were compared with the Mann-Whitney U test.

	Hypertension (n=6)	No Hypertension (n=9)
Baseline Echo Data		
Age	58.0 \pm 11.6	43.3 \pm 9.7*
2-D LV mass index (g/m ²)	87.7 \pm 14.3	67.9 \pm 20.1*
M-mode LV mass index (g/m ²)	75.5 \pm 12.5	73.9 \pm 15.9
EF (%)	71.2 \pm 13.8	65.7 \pm 8.8
LVIT _{BSA} (cc/m ²)	57.1 \pm 18.0	44.6 \pm 8.1
LVOT _{BSA} (cc/m ²)	45.3 \pm 12.5	42.6 \pm 7.3
Stress Echo Data		
EF rest (%)	69.0 \pm 6.5	69.6 \pm 9.7
EF peak (%)	80.0 \pm 5.9	78.5 \pm 11.2
ESV rest (%)	17.5 \pm 5.3	20.6 \pm 9.4
ESV peak (%)	11.1 \pm 4.2	14.8 \pm 10.8

*Only age and LV mass measured by 2-D echo differed between groups. This finding was not unexpected. Data are in agreement with those expressed by others suggesting methods in use to ascertain these numbers are valid.

Nuclear Test

19 of 20 women have completed the nuclear perfusion exercise test with cardiolite. Nuclear Medicine Perfusion Exercise Tests with Cardiolite have demonstrated the difficulty in using this diagnostic method in women. A very large number of women have reports indicating possible defects versus artifacts including breast attenuation and shifting breast attenuation preventing any definitive diagnosis and necessitating cardiac catheterization. This accounts for our very high catheterization rate and demonstrates very effectively the limitations of this procedure for diagnosis in women. 52% or 10 out of 19 participants have a nuclear study that is non-diagnostic because of breast attenuation or shifting breast attenuation. These readings by nuclear medicine are the preliminary readings; however, our blinded readings by Dr. Cote are not yet available because he was recently transferred to Madigan. The computer transfer of data from nuclear medicine here to Madigan is now in place and he will be able to quickly generate the control readings.

Cardiac Catheterization

We have completed 8 cardiac catheterizations as of 10 August 95. Two more cardiac catheterizations are scheduled. Another patient is deciding if she wishes to consent to cardiac catheterization. One patient had a positive catheterization and ultimately underwent angioplasty. There has been one adverse event associated with cardiac catheterization.

GI

As of 31 July 1995 six patients have undergone some testing in gastroenterology. Three patients have been treated with antibiotics for H. Pylori. Two patients are being treated with Prilosec therapy and will be scheduled for repeat EGD. One patient could not have the 24 hour pH test completed because a sinus infection prevented passage of the tube. She will be treated in ENT and rescheduled for testing. Four additional patients are ready to commence GI work-up and will be scheduled in September. One patient has declined to have the GI portion of the study.

Adverse Events

One reportable adverse experience involving a patient occurred post cardiac catheterization. The 36 year old active duty female developed a pseudoaneurysm of the right femoral artery. This complication resulted in hospitalization. She was treated with compression by vascular surgery. Distal femoral flow is within normal limits. The problem appears to be resolving. This is a known complication of cardiac catheterization. This has been reported to the IRC and to HSRRB.

Multiple Medical Problems

A large majority of women enrolled in the study have required referrals to other medical departments such as surgery, rheumatology, endocrinology, neurology, and pulmonary. Pulmonary function tests, ultrasounds of the abdomen, kidneys, etc., EEG, and other tests have been ordered. These patients have additional medical problems that are not related to the study and yet necessitate appropriate intervention.

IV Interim Conclusions

The study has been effectively enrolling patients for three months. Many unforeseen difficulties have made enrollment slower than anticipated. Dr. Calagan's reassignment to Walter Reed and Dr. Cote's reassignment to Madigan have hampered events. Dr. Mark Dorogy will become the Fitzsimons study site primary investigator and Dr. Jennifer Calagan will remain the overall study primary investigator. Nuclear Medicine has installed new computer systems and been down for two week periods. In addition, loss of personnel in nuclear medicine has limited study patient slots. This lack of support is projected to worsen as the base nears closure. The lack of access to other sub-specialties has also been difficult. Completion of the study at Walter Reed is a very viable and reasonable alternative and is projected. An extension is indicated and necessary paper work has been submitted.

Most conclusions are premature at the point in the study. Data has not be analyzed for statistical significance as the study numbers are still too small. However, a definite tendency has emerged in the nuclear medicine readings which are non-diagnostic because of artifact and in particular breast attenuation and shifting breast attenuation. The stress echo appears to correlate more closely with the cardiac catheterization results. It is too soon to do any definitive analysis; however, we will continue to monitor these aspects of the study closely.

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