SUMMARY REPORT FOR THE VIEQUES HEART STUDY EXPERT PANEL REVIEW

(Resumen Ejecutivo en Español)

A MEETING ON JULY 12-13, 2001

SPONSORED BY

THE AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY

AND

THE PONCE SCHOOL OF MEDICINE

NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), a contractor to the Agency for Toxic Substances and Disease Registry (ATSDR), as a general record of discussion for the expert panel review meeting on the Vieques Heart Study. The meeting was co-sponsored by ATSDR and the Ponce School of Medicine.

This report captures the main points of scheduled presentations and highlights discussions among the expert panelists and other participants. This report does not contain a verbatim transcript of all issues discussed during the meeting. Additionally, the report does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. All panelists and participants received a draft copy of the report to verify that the contents of the report accurately reflect the content and tone of discussions at the meeting. Except as specifically noted, no statements in this report represent analyses or positions of ATSDR, CDC, or of ERG.

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
CDC	Centers for Disease Control and Prevention
CT	computerized tomography
EKG	electrocardiogram
EPA	U.S. Environmental Protection Agency
MR	magnetic resonance
PSM	Ponce School of Medicine
TGC	time gain compensation

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EXECUTIVE SUMMARY

BACKGROUND & INTRODUCTION

This report describes the meeting and includes a synthesis of comments and written reports that were individually submitted by each of the external panel members. It does not represent consensus advice to ATSDR. ATSDR will take into account the individual views of the review participants and reach its own recommendations as requested by the White House.

In January 2001, a pilot study comparing the echocardiograms of residents of Vieques and Ponce, Puerto Rico reported substantial valvular abnormalities and pericardial thickening in a large proportion of Vieques residents—findings not seen among Ponce residents. The possible abnormalities noted in the Vieques residents were attributed to "vibro-acoustic disease" (VAD), which had been described in the medical literature by Portuguese investigators. VAD was said to be occurring as the result of noise and vibrations caused by naval exercises on the Island of Vieques. The White House asked the Department of Health and Human Services to investigate the issues raised by the study. The Department, in turn, referred this request to the Agency for Toxic Substances and Disease Registry (ATSDR), which was already investigating environmental public health issues in Vieques. ATSDR received considerable assistance in this work from the Cardiovascular Diseases Branch of the Centers for Disease Control & Prevention (CDC).

Concurrent with this request, the Ponce School of Medicine (PSM), led by President and Dean Dr. Manuel Martínez Maldonado, had begun a more definitive study of possible cardiac abnormalities among Vieques residents. This study sought to overcome methodological problems (e.g., sampling frame, lack of blinding) in the earlier pilot study. On March 29-30, 2001, scientists from ATSDR and CDC met with the PSM investigators and agreed to invite the

assistance of recognized practitioners and scientists in reviewing and interpreting the findings. Reviewers were chosen by consensus. They were experts with international reputations in echocardiography and environmental or cardiovascular epidemiology. San Juan was chosen as the location of the meeting. Because of its extensive experience, the echocardiography "core" laboratory at Mayo Clinic, directed by Dr. Jae K. Oh, was selected to review the echocardiograms.

MEETING ARRANGEMENTS & REPORT ORGANIZATION

Eight accomplished physician-scientists were chosen as reviewers and accepted the invitation to participate. They are referred to herein as "panelists" (see appendices A & B) and are principally from academic institutions. Four panelists are from U.S. universities, two are from Mexico, and two are from Spain. Half of the panelists are specialists in cardiology and echocardiography; the rest are epidemiologists. Other meeting participants included personnel or consultants of PSM and ATSDR, Dr. Jae Oh of Mayo Clinic, and Dr. John Rullán, Secretary of Health of Puerto Rico.

The meeting took place during July 12-13, 2001, in a conference room in the Condado Plaza Hotel in San Juan. The co-chairs of the meeting were Dr. Martínez Maldonado and Dr. David Fleming, Deputy Administrator of ATSDR. The purpose of the meeting was to review the methods, results, and public health significance of the Vieques Heart Study, considering both the PSM and Mayo Clinic Data.

Before the meeting, panelists and other participants were provided with background materials including a specific charge (Appendix C). The meeting followed a prearranged agenda (Appendix D). Panelists provided verbal remarks and written comments on the study. They made individual recommendations on how the Vieques Heart Study data should be interpreted.

Although there was broad agreement on many points, no effort was made to generate a consensus judgment. The panelists' individual written comments have been edited for style, translated (where necessary), and checked for accuracy by the persons who wrote them (Appendix E). A contractor recorded the meeting and summarized and organized the points made by the participants in the various sessions. The meeting minutes thus developed constitute the bulk of this report.

INTRODUCTORY PRESENTATIONS

Dr. Martínez Maldonado noted that Vieques is east-southeast of Puerto Rico, spans roughly 25 square miles, and has roughly 9,000 residents. For approximately the last 60 years, the eastern and western ends of the island have been Navy property. During this time, the Navy has conducted bombing exercises and other war games on the easternmost part of the island.

Dr. Rullán presented background information regarding health issues on Vieques. Changes in the health care system over time have limited the health care available on Vieques. Residents frequently travel to the main island for care. Vieques does less well than the main island on a number of indicators related to public health, including unemployment rates, teenage pregnancy rates, proportion of population receiving prenatal care during the first trimester of pregnancy, per capita income, mortality rates for specific diseases, and self-reported morbidity rates for various types of diseases. Between 1950 and 1991 the Puerto Rico cancer registry was an excellent resource. Following the health care reforms in 1991 and associated cutbacks in certain public health services, health officials have not been able to produce annual reports from the existing cancer registry data. However, an effort to update the cancer registry will soon be complete.

VIEQUES HEART STUDY METHODS & FINDINGS

Dr. Martínez Maldonado and Dr. Carlos Ríos presented the Vieques Heart Study. The study objective was to determine whether an association existed between place of residence (Vieques or Ponce Playa) and morphological cardiovascular changes among commercial fishermen. Investigators sampled randomly from the lists of licensed commercial fishermen from Vieques and from Ponce Playa to obtain 53 and 42 subjects from the two areas, respectively. Investigators measured height, weight, blood pressure and other physical parameters, collected questionnaire data on demographics and possible confounders, and recorded echocardiographic images of subjects. The echocardiograms were read "blindly" (i.e., without knowledge of the site of residence of the particular subject) for pericardial thickness by a group of several experienced PSM cardiologists, with caliper placement done by consensus and by using magnified images.

As noted above, the echocardiograms were re-read by Dr. Oh's group at the Mayo Clinic, who were also blind to the identities of study subjects. Dr. Oh and each of two experienced research sonographers read all studies for pericardial thickness. As with measurements of other parameters, the randomly-assigned, primary sonographer's reading of pericardial thickness was considered final, except in a very few cases in which a substantial discrepancy occurred between the readers. In these cases, Dr. Oh's readings were considered final.

For functional and structural measurements other than pericardial thickness, interobserver agreement among Mayo readers was strong (R-squares of 0.6 to 0.93). However, the interobserver variation on measures of pericardial thickness was weak (R-square only 0.22 for non-magnified images and similarly poor for magnified images). Although there was little intraobserver variation in most parameters measured, the R-square for pericardial thickness (non-magnified) was only 0.3.

For the anatomical and functional parameters measured by both groups, the Ponce and Mayo findings were virtually identical. Moreover, neither data set indicated cardiac pathology among either group of fishermen. Ponce and Mayo findings regarding pericardial thickness were also similar. In neither data set did any subject have an abnormally thick pericardium, based on an upper limit of normal of 2 mm.

By PSM's measurements, the average pericardial thickness was slightly greater among Vieques fishermen than among Ponce Playa fishermen (1.20 mm vs. 1.05 mm), and this difference was statistically significant ($P = 0.03$). The values for pericardial thickness measured by Mayo were within the same range as those measured by PSM, but did not achieve statistical significance when Vieques and Ponce fishermen were compared (0.78 mm vs. 0.82 mm, respectively).

PANEL CONCLUSIONS

The principal conclusion of the panel was that neither the Ponce nor the Mayo readings contained information indicating a cardiac health problem in the fishermen from either location. The initial report of gross valvular pathology from the pilot study was not replicated. All reviewers agreed that there was no clinically relevant difference between Vieques and Ponce Playa subjects in pericardial thickness as had been reported in the pilot study. Moreover, neither the PSM nor the Mayo measurements showed any subject's pericardial thickness to be larger than 2 mm—a reasonable value for the upper limit of normal, based on the published literature.

The PSM study got generally high marks from the panelists regarding study design and statistical analysis. The sampling frame (lists of registered fishermen) was regarded as appropriate, and reviewers generally felt that the response rate was adequate. The fact that reasonably clear-cut hypotheses had been developed beforehand largely obviated concerns about the problem of multiple comparisons. In general, panelists felt that the statistical tests used were appropriately

chosen and employed. Panelists noted that echocardiographic readings were performed with appropriate blinding, including masking of dates, at both PSM and Mayo. More detailed comments and suggestions are described by individual panelists in Appendix E.

With regard to pericardial measurements, the panelists noted that there was substantial measurement error in the technique (i.e., low sensitivity of the echocardiography machine) for measurement of pericardial thickness within the normal range. The lower limit of resolution of trans-thoracic echocardiography was given by the panelists as 1 mm. This value is substantially larger than the average between-group difference of 0.15 mm found by PSM. Moreover, the interobserver and intraobserver reproducibility of the measurements at Mayo was low. Thus, it was not surprising that PSM group reported little correlation between their individual measurements of pericardial thickness and the Mayo measurements (R-square 0.04). With these facts in mind, the panelists opined that the difference between groups in pericardial thickness observed by PSM most likely represented measurement error inherent in the technique used. In any event, no panelist attributed clinical significance to a difference in thickness this small and within the range of values reported by PSM and Mayo.

Pericardial thickness measurements were slightly smaller in the Mayo than in the PSM readings. Nevertheless, it is impossible to state with certainty that either one is “correct,” and it is similarly impossible to rule out that the small numerical differences measured by PSM between Ponce and Vieques fishermen exist. No significant cardiac function changes were detected in either of the populations studied (Vieques vs. Ponce). Thus, even if a small difference in pericardial thickness exists, Vieques fishermen do not appear to have the hemodynamic consequences of a thickened pericardium.

Reviewers noted that the Vieques Heart Study focused specifically on the heart, and it therefore could not rule out other health effects of the Naval exercises, including other potential effects of

noise and vibration. Also, a study of commercial fishermen, a single occupational group, cannot be assumed to be representative of an entire population. In the words of one panelist, "further studies and ongoing monitoring are needed of … morbidity, mortality, and risk profiles of Vieques citizens as current plans are implemented to reduce their noise exposure and to improve the economy, health care, and public health of the area." That said, however, reviewers generally did not feel that further studies of pericardial thickness would be of value.

It was recommended that the Ponce and Mayo Clinic measurements be published jointly. This would address as thoroughly as possible the issues of appropriate methodology, assessment of pericardial thickness, and the clinical significance of the results.

SUMMARY CONCLUSION

The well-executed PSM study does not support the existence of cardiac pathology among Vieques fishermen. Because of the inability of trans-thoracic echocardiography to measure reliably the small differences found, the differences reported are likely due to measurement error (intrinsic to the technique, not the scientists who used it). This fact almost certainly accounts for the different results obtained when Mayo readings of pericardial thickness are used in place of PSM readings. The Vieques Heart Study represents a valuable contribution to scientific knowledge regarding the use of echocardiography and should be published in the peer-reviewed scientific literature.

RESUMEN EJECUTIVO

ANTECEDENTES E INTRODUCCIÓN

Este informe describe la reunión e incluye una síntesis de los comentarios e informes escritos sometidos por cada uno de los miembros del panel externo. Se debe aclarar que el informe no representa un consejo en consenso a la Agencia de Sustancia Tóxicas y Registro de Enfermedades (ATSDR por sus siglas en inglés). La ATSDR tomará en cuenta las opiniones de los participantes y hará sus propias recomendaciones de acuerdo a lo solicitado por la Casa Blanca.

En enero del 2001, un estudio piloto de comparación de ecocardiogramas de residentes de Vieques y Ponce, Puerto Rico, reportó anomalías valvulares y engrosamiento pericárdico sustancial en una gran proporción en los residentes de Vieques – no así con los residentes de Ponce. Estas posibles anomalías en los residentes de Vieques se atribuyeron a "enfermedad vibro acústica" (VAD por sus siglas en inglés), que ha sido descrita en la literatura médica por investigadores portugueses. Se sugirió que la VAD era el resultado del ruido y las vibraciones causadas por los ejercicios navales en la isla de Vieques. La Casa Blanca pidió al Departamento de Salud y Servicios Humanos que investigara la situación presentada en el estudio. El Departamento, a su vez, refirió la solicitud a la Agencia de Sustancias Tóxicas y Registro de Enfermedades (ATSDR), la cual se encontraba ya investigando situaciones de salud pública ambientales en Vieques. La ATSDR recibió asistencia considerable en este trabajo del Grupo de Enfermedades Cardiovasculares del Centro de Control y Prevención de Enfermedades (CDC por sus siglas en inglés).

Coincidentemente con esta solicitud, la Escuela de Medicina de Ponce (PSM), dirigida por su presidente y decano Dr. Manuel Martínez Maldonado, había comenzado un estudio más definitivo de las causas posibles de las anormalidades cardíacas entre los residentes de Vieques.

Este estudio tenía la intención de reducir los problemas metodológicos (por ejemplo, enmarcado de las muestras, carencia de “ensayos a ciegas” (“blinding”), etc.) del estudio piloto anterior. El 29-30 de marzo del 2001, científicos de la ATSDR y del CDC se reunieron con los investigadores de la PSM y acordaron de pedir la colaboración de médicos practicantes y científicos reconocidos en la revisión y en la interpretación de los resultados de las investigaciones. Los revisores se escogieron por consenso. Estos revisores eran expertos de reputación internacional en ecocardiografía y epidemiología ambiental o cardiovascular. San Juan fue escogido como la sede de la reunión. Debido a su gran experiencia, el laboratorio ecocardiográfíco medular (“core”) de la Clínica Mayo dirigido por el Dr. Jae K. Oh, fue seleccionado para revisar los ecocardiogramas.

ARREGLOS PARA LAS REUNIONES Y ORGANIZACIÓN

Ocho médicos-científicos experimentados fueron escogidos como revisores y aceptaron la invitación para participar. A partir de ahora nos referiremos a ellos como los "panelistas" (ver Apéndices A & B). En su mayoría, estos médicos pertenecen a instituciones académicas. Cuatro panelistas son de universidades de Estados Unidos, dos son de México, y dos son de España. La mitad de los panelistas son especialistas en cardiología y ecocardiografía, y el resto son epidemiólogos. Entre los otros participantes se encuentran incluidos parte del personal de la PSM y la ATSDR, además del Dr. Jae Oh de la Clínica Mayo, y el Dr. John Rullán, Secretario de Salud de Puerto Rico.

La reunión se efectuó durante los días 12 y 13 de julio del 2001 en una sala de conferencias del Condado Plaza Hotel en San Juan. Los presidentes de la reunión fueron los doctores Martínez Maldonado y David Fleming, Administrador Suplente de la ATSDR. El propósito de la reunión fue la revisión de los métodos, resultados y el significado de salubridad pública en el Estudio Cardíaco de Vieques, considerando tanto los datos de PSM, como los de la Clínica Mayo.

Antes de la reunión, se proporcionó a los panelistas y a los otros participantes material de referencia, incluyendo instrucciones específicas (Apéndice C). La reunión estuvo sujeta a una agenda preparada con antelación (Apéndice D). Los panelistas proporcionaron observaciones verbales y comentarios escritos sobre el estudio. Los panelistas hicieron recomendaciones individuales acerca de la forma en la que los datos del Estudio del Corazón de Vieques deberían ser interpretados. Aunque hubo amplio acuerdo en una gran cantidad de tópicos, no se hizo esfuerzo por alcanzar un consenso. El estilo, la traducción (donde fue necesario) y la fidelidad de los comentarios individuales escritos de los panelistas fueron editados y comprobados por las personas que los escribieron. (Apéndice E). Un contratista grabó la reunión y resumió y organizó los planteamientos hechos por los participantes en las diferentes sesiones. Las actas de la reunión forman el grueso de este informe.

INTRODUCCIÓN Y PRESENTACIONES

El Dr. Martínez Maldonado señaló que Vieques se encuentra al este–sudeste de la isla de Puerto Rico, que abarca alrededor de 25 millas cuadradas y tiene aproximadamente 9,000 residentes. Durante aproximadamente los últimos 60 años, los extremos este y oeste de la isla han sido propiedad de la Marina. Durante la totalidad de este lapso, la Marina ha conducido ejercicios de bombardeos y otras tácticas de guerra en la parte más oriental de la isla.

El Dr. Rullán presentó el trasfondo de los problemas de Vieques. Cambios en el sistema de salud asistencial gubernamental en los últimos años han limitado los servicios de salud disponible en Vieques. Los residentes frecuentemente viajan hasta la isla principal para obtener atención médica. Vieques tiene una puntuación menor que la isla principal en varios de los indicadores relacionados con la salud pública, incluyendo tasas de desempleo, adolescentes embarazados, la proporción de la población que recibe cuidado prenatal durante el primer trimestre del embarazo, ingresos per cápita, tasas de mortalidad en relación con enfermedades específicas y tasas de morbilidad de enfermedades auto-reportables. Entre 1950 y 1991 el registro de cáncer de Puerto

Rico fue una excelente fuente de información. Después de las reformas de salud de 1991 y los cortes asociados con ciertos servicios de salud pública, los oficiales de salud no han sido capaces de producir informes anuales de los datos de cáncer existentes. Sin embargo, se espera que pronto se pueda actualizar el registro de cáncer.

RESULTADOS Y MÉTODOS DEL ESTUDIO DEL CORAZÓN DE VIEQUES

Los doctores Martínez Maldonado y Carlos Ríos presentaron el Estudio del Corazón de Vieques. El objetivo del estudio fue determinar si existía alguna asociación entre el lugar de residencia (Vieques o Playa Ponce) y los cambios cardiovasculares morfológicos entre los pescadores comerciales. Los investigadores tomaron muestras al azar de la lista de pescadores comerciales licenciados de Vieques y Playa Ponce para obtener 53 y 42 muestras respectivamente de las dos áreas. Los investigadores midieron el peso, la presión sanguínea y otros parámetros físicos, reunieron datos de cuestionarios demográficos y grabaron ecocardiogramas de los sujetos de estudio. Los ecocardiogramas fueron leídos a ciegas (sin saber su procedencia) por un grupo de varios cardiólogos experimentados de la PSM en búsqueda de engrosamiento pericárdico, con la colocación de los calibradores llevada a cabo por consenso y usando imágenes aumentadas.

Como describimos anteriormente, los ecocardiogramas fueron leídos por el grupo del doctor Oh en la Clínica Mayo. Sin saber cuál era el lugar de procedencia de los sujetos, el Dr. Oh y cada uno de los otros dos experimentados técnicos sonográficos leyeron todos los estudios en búsqueda de engrosamiento pericárdico. Tal como se hizo con las medidas de los otros parámetros, la lectura inicial de los sonógrafos, asignadas al azar, en busca de engrosamiento pericárdico fue considerada final, excepto en limitadas ocasiones en las cuales ocurrió discrepancia substancial entre las lecturas. En tales casos, la lectura del Dr. Oh fue la considerada como final y válida.

En contraste con las medidas del engrosamiento pericárdico, las medidas funcionales y estructurales de la Mayo tuvieron una fuerte correlación interobservador (R-cuadrados de 0.6 a 0.93). Sin embargo, la variación interobservadora en medidas de engrosamiento pericárdico fue débil (R-cuadrado solamente 0.22 para imágenes no aumentadas y similarmente pobres para imágenes aumentadas). Aunque hubo poca variación intraobservadora en la mayoría de los parámetros medidos, el R-cuadrado para engrosamiento pericárdico (no-aumentado) fue solamente 0.3.

Para los parámetros anatómicos y funcionales medidos por ambos grupos, los resultados de Ponce y Mayo fueron virtualmente idénticos. Por otra parte, ninguno de los datos indicó patología cardiaca entre ninguno de los grupos de pescadores. Los resultados de Ponce y Mayo también fueron similares en relación con las lecturas del engrosamiento pericárdico. En ninguno de los datos se notó la existencia de engrosamiento anormal del pericardio, basado en un límite superior normal de 2 mm.

De acuerdo con las medidas de PSM, el promedio del grosor fue ligeramente mayor entre los pescadores de Vieques que entre la población de pescadores de Playa Ponce (1.20 mm vs. 1.05 mm), y esta diferencia fue estadísticamente significativa (P = 0.03). Los valores para el engrosamiento pericárdico medido por Mayo estuvieron dentro del mismo rango que los de PSM, pero no alcanzaron significado estadístico cuando los pescadores de Vieques y Ponce fueron comparados (0.78 mm vs. 0.82 mm, respectivamente).

CONCLUSIONES DEL PANEL

La conclusión principal del panel fue que los resultados de Ponce o de Mayo no contienen información que indique que existe al momento un problema de salud cardíaca en los pescadores de ninguna de las localizaciones estudiadas. El informe inicial de la patología gruesa valvular informada en el estudio piloto no fue corroborado. Todos los revisores estuvieron de acuerdo en

que no existía ninguna diferencia de relevancia clínica entre los sujetos de Vieques y la Playa de Ponce en lo referente al engrosamiento pericárdico, tal y como fue reportado en el informe piloto. Además, ni las medidas de la PSM ni las medidas de Mayo mostraron ningún engrosamiento pericárdico en los sujetos estudiados mayor de 2 mm – un valor razonable para el límite normal, basado en la literatura publicada.

El estudio de la PSM recibió encomios substanciales de parte de los panelistas en relación con el análisis estadístico y el diseño del estudio. El marco de las muestras (lista de pescadores registrados) fue considerado como apropiado, y los revisores acordaron que la tasa de respuesta fue adecuada. El hecho de que una hipótesis netamente definida había sido desarrollada de antemano, en gran manera obviaba las preocupaciones acerca del problema de comparaciones múltiples. En general, los panelistas acordaron en que las pruebas estadísticas usadas fueron escogidas y usadas apropiadamente. Los panelistas aseveraron que las lecturas de ecocardiografía fueron llevadas a cabo con los parámetros apropiados, incluyendo la no-revelación de las fechas ni del lugar de procedencia del ecocardiograma, tanto al grupo de PSM como al de la Clínica Mayo. Mayores detalles y sugerencias se encuentran descritos por parte de los panelistas individuales en el Apéndice E.

En lo relacionado a las medidas pericárdicas, los panelistas aseveraron que había errores de medidas substanciales en las técnicas (la sensibilidad de la máquina) de medida del espesamiento pericardial dentro del índice normal. El límite menor de resolución de la ecocardiografía trans-toráxica fue proporcionado por los panelistas como 1 mm. Este valor es substancialmente mayor que el promedio entre la diferencia de grupos de 0.15 mm encontrado por la PSM. Por otra parte, la reproducibilidad del interobservador y del intraobservador de las medidas de Mayo fue baja. Por tanto, no fue sorprendente que el grupo PSM reportó una correlación pequeña entre sus medidas de espesamiento pericardial y las medidas de Mayo (R-cuadrado 0.04). Tomando esto en consideración, la opinión de los panelistas fue que la diferencia entre los grupos en lo referente al engrosamiento pericárdico observada por PSM posiblemente representaba errores de medida

inherentes a la técnica usada. En cualquier caso, ningún panelista atribuyó significado clínico a la diferencia en un engrosamiento tan pequeño y dentro del índice de valores reportados por la PSM y Mayo.

Las lecturas en las medidas de engrosamiento pericárdico fueron ligeramente menores para Mayo que para la PSM. Sin embargo, es posible declarar con certidumbre que ninguna de las dos es incorrecta, y que es similarmente imposible descartar que la pequeña diferencia numérica entre las medidas del PSM entre Ponce y los pescadores de Vieques existe. No se detectó cambio alguno en las funciones cardiacas de las poblaciones estudiadas (Vieques vs. Ponce). Por lo tanto, aunque existiese la pequeña diferencia en el engrosamiento pericárdico, los pescadores de Vieques no aparentan tener las consecuencias hemodinámicas de un pericardio grueso.

Los revisores comentaron que el Estudio del Corazón de Vieques se concentró específicamente en el corazón, y que por lo tanto no se podía descartar que hubiese efectos de los ejercicios navales en otras áreas de la salud, incluyendo efectos potenciales debido al ruido y a las vibraciones. Además se declaró que no se puede asumir que un estudio de solamente los pescadores, un grupo ocupacional único, es representativo la totalidad de la población general de Vieques. En las palabras de uno de los panelistas: "...más estudios y monitoreo continuo son necesarios, además de estudios de... la morbilidad, y los perfiles de riesgo de los habitantes de Vieques, al tiempo que se implementan planes para reducir la exposición a ruidos y para mejorar la economía, el cuidado de la salud y la salud pública del área." Habiendo dicho esto, sin embargo, los revisores en general no consideraron que fueran necesarios más estudios para determinar el engrosamiento pericárdico.

Se recomendó que las medidas de Ponce y la Clínica Mayo fueran publicadas en conjunto para aclarar para todos los ecocardiografistas cual es la metodología apropiada para la evaluación del engrosamiento pericárdico, y el significado clínico de los resultados que usan esta tecnología.

CONCLUSIÓN DEL RESUMEN

El estudio bien ejecutado de la PSM no apoya la existencia de patologías cardíacas entre los pescadores de Vieques. Debido a la incapacidad del ecocardiograma trans-toráxico para medir confiablemente las pequeñas diferencias en los resultados encontrados, las diferencias reportadas son probablemente debidas a errores del método de medida utilizado (intrínseco a la técnica, no a los científicos que la usaron). Este hecho casi ciertamente explica la diferencia entre las lecturas de la PSM y la Mayo. El Estudio del Corazón de Vieques representa una contribución valiosa al conocimiento científico en lo relacionado con el uso de la ecocardiografía y debería ser publicado en una revista científica de revisión por pares (“peer review journal”).

1.0 INTRODUCTION

This report is a record of the discussion during an expert panel review meeting held in San Juan, Puerto Rico, on July 12–13, 2001. The meeting was co-sponsored by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Ponce School of Medicine (PSM). The Cardiovascular Diseases Branch of the Centers for Disease Control and Prevention (CDC) also contributed substantially to this effort.

The meeting was held to review possible cardiac abnormalities among commercial fishermen who reside on the island of Vieques. This section of the report provides background information on the expert panel review meeting. Later sections document the technical discussions that took place among the reviewers and other participants.

This introduction, Section 1.1, provides background information on Vieques and the research under review. Section 1.2 describes the process by which the expert panelists were selected. Section 1.3 reviews the meeting agenda, and Section 1.4 outlines the organization of the rest of this summary report.

1.1 Background

The island of Vieques lies east of the main island of Puerto Rico and has approximately 9,000 residents. For several decades, the United States Navy (Navy) has used the far eastern end of Vieques as a practice ground for training exercises. The exercises have involved the use of explosive ordnance (bombs, artillery shells, and other explosive devices), which cause noise and vibration evident to Vieques residents.

Concern has been expressed regarding possible adverse impact of Navy exercises on the health of Vieques residents. This concern has been particularly great during the last 2 years. One of the

issues raised has been whether noise and vibration could have had an adverse health impact on island residents. Dr. N. Castelo-Branco and others in Portugal have described a syndrome of cardiologic, neurologic, and immunologic findings in aircraft workers that they labeled "vibroacoustic disease."[1] Cardiac abnormalities noted by Dr. Castelo-Branco and colleagues included pericardial thickening and valvular abnormalities observable by echocardiography.[2]

Acting on the hypothesis that Vieques residents might have developed abnormalities similar to those observed by the Portugese investigators, PSM investigators used commercial fishermen' trade association lists to recruit subjects in Vieques and a comparison group of fishermen in Ponce. Subjects were studied by echocardiography, with readings done by the PSM investigators. At the request of ATSDR and PSM, Dr. J. K. Oh of the Mayo Clinic in Rochester, Minnesota, performed blind independent readings of the same data. The PSM and Mayo Clinic investigators reported their findings at the expert panel review meeting (see Section 2.0). For the remainder of this report, the research conducted by PSM is referred to as "the Vieques Heart Study."

Earlier this year, the White House charged the Department of Health and Human Services (HHS) with scientifically evaluating reports of cardiovascular abnormalities occurring among residents of Vieques and potentially related to naval exercises. The Secretary of HHS delegated this task to ATSDR. The Governor of Puerto Rico also asked ATSDR to participate in this assessment. To respond to these requests, ATSDR has worked cooperatively with PSM investigators to evaluate the recent study of cardiac abnormalities—research that has raised a number of important questions on the frontiers of echocardiography, cardiology, and environmental epidemiology. The findings of this expert panel review meeting will be a critical input to ATSDR's response to the charge from the White House.

1.2 The Expert Panel

To organize a comprehensive and fair review, ATSDR and PSM each nominated candidates to serve as expert panelists for this meeting. The co-sponsors reviewed nominees and, by consensus, chose eight internationally recognized scientists to serve as the expert panelists. The final expert panelists have demonstrated expertise in one or more of the following fields: cardiology, echocardiography, cardiovascular epidemiology, or environmental epidemiology. These experts came from Mexico (2 panelists), Spain (2 panelists) and the United States (4 panelists) and had a variety of institutional affiliations (mostly academic). Although they were reimbursed for travel expenses, none of the co-sponsors paid the experts for the time spent during the meeting or reviewing reports. The remainder of this report refers to these eight individuals as *panelists*. Appendix A lists the eight expert panelists and their affiliations. Appendix B contains brief biographical sketches of the panelists.

Fourteen other individuals participated in the expert panel review meeting. These other participants included several representatives of the meeting co-sponsors: six individuals from ATSDR and five from PSM (including Dr. Julio Pérez, acting as consultant to PSM). They also included Dr. John Rullán, the Puerto Rico Secretary of Health, and Dr. J. K. Oh, Chief of the Echocardiography Core Lab at the Mayo Clinic. The remainder of this report refers to these 14 individuals as *participants*. Appendix A lists the names and affiliations of the 14 participants, and Appendix B presents brief biographical sketches of them.

Prior to the meeting, all panelists and participants received a package of background materials[2,3,4,5] as well as a "charge to the reviewers" (Appendix C) that included both background information and a list of questions that the technical discussions at the meeting would be asked to address. The charge focused the reviewers' comments on four question areas: (1) study design and ascertainment, (2) echocardiographic measurements, (3) statistical analysis, and (4) interpretation and inference. The reviewers and participants did not receive written materials

describing the PSM research on potential cardiovascular abnormalities among Vieques commercial fishermen (i.e., the Vieques Heart Study), because that work has not yet been published. For this reason, principal investigators from PSM and the Mayo Clinic gave detailed technical presentations on their research (see Section 2) before reviewers commented on the study.

1.3 The Expert Panel Review Meeting

The 2-day expert panel meeting took place at a conference room in the Hotel Condado Plaza in San Juan, Puerto Rico, on July 12–13, 2001. Presentations and discussions at the meeting generally followed the agenda (Appendix D). Two participants—Dr. David Fleming (ATSDR) and Dr. Manuel Martínez Maldonado (PSM)—acted as meeting co-chairs and moderators for the discussions among the panelists and participants.

As the agenda shows, the meeting began with introductory remarks and background presentations from four participants. Summaries of these presentations are provided below. The technical presentations on the Vieques Heart Study followed the opening remarks. For the remainder of the meeting, the panelists engaged in free-flowing discussions organized around the four question areas in the charge. During the discussions, reviewers and participants offered their individual perspectives on the Vieques Heart Study and associated topics. Although panelists agreed on many points, no effort was made to reach an absolute consensus on any issue. At the end of the meeting, the reviewers and some participants prepared written summaries of their comments (Appendix E).

Summaries of the four background presentations follow (refer to Section 2 for summaries of the technical presentations on the Vieques Heart Study):

Dr. Manuel Martínez Maldonado, President and Dean, PSM. Dr. Martínez Maldonado is

the principal investigator of the Vieques Heart Study. He provided background information on how and why PSM initiated the Vieques Heart Study. He stated that PSM investigators decided to conduct the study after being approached by a group of physicians, including an *ad honorem* PSM faculty member, with preliminary data on possible health effects associated with noise and vibration. He noted that, in November 2000, a PSM-appointed committee of researchers designed a study to investigate further the preliminary data.

Dr. Martínez Maldonado reviewed in general how the study was implemented. He stressed, for instance, that his primary concern was to conduct the study following rigorous scientific methods. Accordingly, the researchers used a new Agilent echocardiogram machine. In addition, Dr. Martínez Maldonado said that while working on the project, he tried to ensure that all researchers remained objective and impartial.

Finally, Dr. Martínez Maldonado provided some background information on Vieques. The island lies east-southeast of Puerto Rico, spans roughly 25 square miles, and has roughly 9,000 residents. The eastern and western ends of the island have been Navy property, and the Navy has conducted bombing exercises and other war games on the easternmost part of the island for the last 60 years. Dr. Rullán provided additional background information on Vieques during his presentation, summarized below.

*Dr. David Fleming, Deputy Administrator, ATSDR and Deputy Director for Science & Public Health, CDC*. Dr. Fleming offered brief remarks on the political and scientific issues related to Vieques, encouraging participants and panelists to focus their discussions strictly on science. Although he acknowledged that the future of Vieques is the subject of intense political debate, he stressed that the panelists are not being asked to offer solutions on this matter. Dr. Fleming also stressed that the purpose of the meeting was strictly for the expert panelists to provide their individual opinions on the scientific issues

relevant to the Vieques Heart Study, without attempting to reach consensus on any issue. After making these statements, at Dr. Fleming's invitation, panelists and participants introduced themselves, noting their affiliations and areas of expertise.

Dr. Edwin M. Kilbourne, Associate Administrator for Toxic Substances & Public Health, ATSDR. Dr. Kilbourne spoke briefly about the goal of the meeting and raised the subject of the earlier pilot study that preceded the Vieques Heart Study. He indicated that the purpose of the meeting was to solicit individual expert opinions on issues relevant to the Vieques Heart Study, whether or not those comments were consistent with others offered. Dr. Kilbourne encouraged the panelists and participants to provide verbal input throughout the meeting, and he added that panelists would be asked to submit written comments as well. Dr. Kilbourne asked that panelists and participants frame their discussions around the four question areas listed in the charge (Appendix C). Discussions on topics outside these question areas were permitted, but not encouraged.

Dr. Kilbourne then clarified some issues surrounding the earlier pilot study by Drs. Torres Aguiar, Castelo Branco and others involving echocardiographic data that led PSM to initiate the Vieques Heart Study.[3] First, Dr. Kilbourne emphasized that the earlier investigation was not the focus of the meeting; the panelists' discussions should focus on the subsequent data generated by PSM. He asked, however, that the panelists submit written comments on the earlier study, because ATSDR must address the public health implications of both this earlier study and the Vieques Heart Study data when responding to the White House inquiry regarding cardiovascular abnormalities in Vieques.

Finally, regarding the availability of the Vieques Heart Study data, Dr. Kilbourne stated that ATSDR and PSM are still analyzing and reviewing the results. Thus, no written summaries of the study are available for distribution. However, he added that the PSM investigators might be able to supplement their presentation by generating selected data

summaries during the meeting, if necessary.

Dr. John Rullán, Secretary of Health, Puerto Rico Department of Health. Dr. Rullán's presentation addressed three topics: (1) changes in the Puerto Rico health care system that have affected access to health care in Vieques, (2) findings from Puerto Rico's National Health Review Survey, and (3) cancer statistics for Puerto Rico. First, Dr. Rullán described how the public health care system in Puerto Rico has changed over the years, focusing on how these changes have affected access to health care on Vieques. Specifically, he noted that the 1993 privatization of health care in Puerto Rico caused primary care centers throughout the Commonwealth to cut many services. Dr. Rullán recalled that services at the primary care center in Vieques were cut dramatically throughout the 1990s. The primary care center now operates without a laboratory, delivery rooms, and other services it once provided, causing many residents to travel to the main island of Puerto Rico to seek certain types of medical care. However, Dr. Rullán indicated that services offered by the primary care center in Vieques are now expanding, and he listed specific examples of scheduled improvements.

Second, Dr. Rullán presented a series of demographic and statistical data comparing the population in Vieques to the entire population of Puerto Rico. These data came from several sources, including the 1990 United States Census and a 1998 health interview survey administered by the Puerto Rico School of Public Health. Dr. Rullán explained that this latter data source is similar to the National Health Interview Survey, but was tailored to the population of Puerto Rico. Data from the health survey are based on responses from 250 households on Vieques, which are felt to be representative of the entire island's population. Dr. Rullán then presented numerous statistics including, but not limited to, unemployment rates, teenage pregnancy rates, proportion of population receiving prenatal care during the first trimester, per capita income, mortality rates for specific diseases, and self-reported morbidity rates for different types of diseases.

Third, Dr. Rullán reviewed the Puerto Rico Department of Health's recent efforts to update its cancer registry. For background, Dr. Rullán said that between 1950 and 1991 the Puerto Rico cancer registry was an excellent resource. Following the 1991 health care reforms and associated cutbacks in certain public health services, health officials have not been able to produce annual reports from the existing cancer registry data, and the cancer registry for Puerto Rico is not yet updated. Recognizing the value of accurate cancer registry data, the Puerto Rico Department of Health, in collaboration with CDC, has worked to update the cancer registry for the years 1997–2000. Dr. Rullán reported the progress of the updates, indicating that he expects in August 2001 to report 1997 cancer incidence and mortality data for Vieques and all of Puerto Rico. Dr. Rullán indicated that preliminary results suggest that cancer mortality at Vieques is higher than that of Puerto Rico. Finally, Dr. Rullán acknowledged that interpreting these and other health outcome data for Vieques is complicated by various confounding factors, such as the limited access to, and the quality of, health care on the island.*

At the end of his presentation, Dr. Rullán and another participant provided some background information on Navy operations at Vieques. Referring to a map of Vieques, the participant indicated where the Navy exercises take place and said that, prior to 1999, these exercises occurred from sea, air, and land 180 days per year. He indicated that Navy exercises temporarily ceased in 1999, when a watchman was killed by an errant bomb dropped on the island. Since 1999, exercises have been extremely limited. This participant offered additional information on legal issues related to noises generated by the Navy exercises.

Following his presentation, Dr. Rullán answered several questions about the health outcome data he presented. When one panelist asked if data are available on trends in

* When answering questions later in the meeting, Dr. Rullán noted that a 1998 survey found that 72% of the Vieques residents who are covered under public health care have never used their health cards.

cancer rates over time; Dr. Rullán responded that such data should be available after the cancer registries are updated. He added that data trends might determine whether further research into cancer incidence and mortality (e.g., case control studies) is warranted. Another panelist asked if the cancer registry data are organized in a fashion that will allow Puerto Rico Department of Health to compare data for Vieques with data for other communities with similar characteristics, such as per capita income and socioeconomic status. Dr. Rullán responded that such data are not currently available, but likely will be within several months. Another panelist asked if anyone could elaborate on the ancestry and primary occupations of the Vieques population. A participant noted that the population of Vieques is believed to be of the same heritage as the population of Puerto Rico; he added that 105 of the roughly 9,000 residents of Vieques are registered commercial fishermen.

1.4 Report Organization

The remainder of this report is organized according to the four question areas listed in the charge to the reviewers. First, Section 2 reviews two technical presentations given at the beginning of the meeting. Then, Sections 3, 4, 5, and 6 summarize the discussions on study design and data ascertainment, echocardiographic measurements, statistical analysis, and interpretation and inference, respectively. At the end of the meeting, the panelists were asked to summarize their overall impressions of the Vieques Heart Study in writing and then share their final thoughts with the group. Section 6 summarizes these final remarks along with the panelists' comments on interpretation and inference.

All tables cited in the text appear at the end of the section in which they are mentioned. Full citations for references are provided in Section 7.

2.0 TECHNICAL PRESENTATIONS ON THE VIEQUES HEART STUDY

This section summarizes the two technical presentations specifically addressing the Vieques Heart Study. Because no written materials were available on the Vieques Heart Study, the content of the technical presentations largely formed the basis for the panelists' reviews. Accordingly, this report summarizes the two presentations in detail, as well as the question and answer sessions that followed. The presentations are summarized in the order in which they were given.

Note that the content of this section is almost entirely based on the presentations of two *participants*. Sections 3 through 6 of this report summarize the *panelists'* comments and findings regarding the information provided.

2.1 Summary of Presentation by Dr. Oh, Mayo Clinic

Dr. Oh opened his presentation by reviewing his and the Mayo Clinic's experience with echocardiography. He indicated that the "Echo Lab" at the Mayo Clinic conducts 200 echocardiographic examinations daily and is currently staffed by 80 sonographers, including 7 research sonographers, who have performed at least 3 years of clinical sonography to receive that designation. In addition, Dr. Oh indicated that he manages the Mayo Clinic's Echo Core Lab, established specifically to read and interpret echocardiographic results for clinical trials. For the Vieques Heart Study, the Core Lab recruited three experienced research sonographers to read PSM's echocardiographic images, and all three operated under Dr. Oh's direct supervision. The following subsections review the main topics of Dr. Oh's presentation.

2.1.1 Background on Echocardiography

Dr. Oh briefly reviewed the application of echocardiography, focusing exclusively on transthoracic echocardiography—the type used by PSM investigators in the Vieques Heart Study. Dr. Oh explained that echocardiographic readings can be taken in various modalities, such as M-mode, 2-dimensional imaging, and Doppler echocardiography. For perspective, Dr. Oh displayed sample outputs from these three modalities, all of which were used in the Vieques Heart Study:

- *2-dimensional echocardiography*. Dr. Oh showed several videos of 2-dimensional echocardiographic readings from both the parasternal and apical views, as well as different transducer orientations for these views. He identified the different heart structures visible from these views and listed various dimensions and parameters that can be calculated from these images.

- *M-mode echocardiography*. Dr. Oh displayed several sample images obtained from M-mode echocardiography. He indicated the dimensions that the Mayo researchers routinely measure using M-mode (e.g., aortic valve opening, left atrial dimension, left ventricle dimension). Dr. Oh noted that his research team typically does not measure pericardial thickness using M-mode echocardiography, primarily because pericardial disease typically manifests as hemodynamic problems and impaired diastolic function, which can be assessed directly with Doppler echocardiographic measurements or other tests.

- *Doppler echocardiography*. Dr. Oh explained how Doppler echocardiography is used to determine the velocity of blood through various heart structures and showed some sample outputs. Several hemodynamic parameters can then be calculated from the velocity measurements. These parameters include stroke volume, cardiac output, and intracardiac pressures.

2.1.2 Mayo Clinic's Readings of Echocardiographic Images from the Vieques Heart Study (See appendix E.9)

Following his background presentation on echocardiography, Dr. Oh commented specifically on how his research team read the echocardiograms from the Vieques Heart Study, (copies of which the PSM investigators provided on 7 CD-ROMs). The images did not include any reference to the subjects from which they were collected (i.e., the Mayo readers were "blinded" to the subjects). The Mayo Clinic was not involved with the original acquisition of the echocardiograms in the Vieques Heart Study. Dr. Oh emphasized that his team, comprised of himself and three research sonographers, employed a standardized approach to process the data. The approach was designed to generate the data requested by ATSDR and PSM, while also characterizing intra-observer and inter-observer variability in measurements, as summarized below:

Approach for measuring parameters other than pericardial thickness. The research team included two primary sonographers and a secondary sonographer. The secondary sonographer received the echocardiographic images, randomly divided the images into two sets, and assigned the sets to the two primary sonographers for reading. The primary sonographers measured a large set of parameters, such as left ventricular dimension at different points in the cardiac cycle. To characterize intra-observer variability in these measurements, both sonographers re-read 10 randomly selected echocardiograms from their original set, but more than 10 days after the first readings were made. To characterize inter-observer variability, the secondary sonographer measured 30 randomly selected echocardiographic images, or roughly one-third of the total echocardiograms reviewed. Dr. Oh later presented the intra- and inter-observer variability data for measuring parameters other than pericardial thickness (see Section 2.1.3).

Finally, Dr. Oh visually reviewed the sonographers' data, resolved any significant data

discrepancies observed between the two sonographers' readings, and conducted random quality control checks. Dr. Oh entered the primary sonographers' measurements into the final data set, except in the few cases when significant discrepancies were observed between the primary and secondary sonographer. In these cases, Dr. Oh's measurements were used as the final result.

Approach for measuring pericardial thickness. Given the emphasis on pericardial thickening, Dr. Oh implemented a more rigorous reading procedure for determining pericardial thickness than that used for measuring other structural and functional parameters. Rather than having each of the two research sonographers read half of the total images, Dr. Oh instructed both sonographers to measure pericardial thickness in every echocardiographic image provided by PSM. Even though two sonographers measured pericardial thickness on every image, all images had a randomly assigned "primary" and "secondary" sonographer. Additionally, Dr. Oh read every image for pericardial thickness.

As with the measurements for other parameters (see previous bulleted item), the primary sonographer's readings of pericardial thickness were considered the final results, except in cases with significant discrepancies between the readers. As stated, in these cases Dr. Oh's readings were considered final. He indicated that this occurred in only a small subset of the recordings Mayo reviewed

Measurement of mitral leaflet thickness. At the request of a consultant to PSM, Dr. Oh's research team also measured mitral leaflet thickness. These measurements were conducted after the measurements listed above were completed. Time constraints prevented Dr. Oh from having two sonographers make these measurements. He did not discuss these measures further.

After describing the general approach used to read the echocardiographic images, Dr. Oh spoke more specifically on how sonographers read each individual recording. He indicated that sonographers made all readings by loading the echocardiographic images onto a Digisonic workstation, which was calibrated for each image being viewed. Dr. Oh noted that the calibration step was necessary because the echocardiograms provided were collected from different views (i.e., parasternal and apical) and different orientations. At PSM's request, the Mayo sonographers always measured pericardial thickness at end diastole, as determined by the output from the electrocardiogram (EKG) on the echocardiographic image. Dr. Oh instructed the sonographers to measure pericardial thickness in at least three different cardiac cycles for each image. The thicknesses were measured visually using calipers, both in unmagnified and magnified views.

2.1.3 Variability in Measuring Pericardial Thickness Using Echocardiography

To characterize the precision of the sonographers' measurements, Dr. Oh determined both inter-observer and intra-observer variability from data generated during duplicate measurements. First, Dr. Oh presented data on inter-observer variability; that is, comparisons of measurements that the two sonographers reported for the same echocardiographic images. These data suggested relatively strong agreement (R^2 values ranging from 0.6 to 0.93) between the two sonographers for structural parameters (e.g., left ventricular mass) and functional parameters (e.g., deceleration time).However, the agreement for measures of pericardial thickness from nonmagnified images was weak ($R^2 = 0.22$). Dr. Oh also indicated that the agreement was weak for reading pericardial thickness from magnified images, but he did not present any data characterizing the correlation.

Second, Dr. Oh presented data on intra-observer variability, but only for a limited set of measures. He indicated that agreement between sonographers on measurements of left

ventricular end-diastolic dimension was excellent ($R^2 = 0.93$), while the agreement between sonographers on measurements of pericardial thickness from nonmagnified images was relatively poor ($R^2 = 0.30$). Dr. Oh noted that the intra-observer variability was also weak for measuring pericardial thickness in magnified images, although he did not provide the correlation statistics.

Some panelists asked Dr. Oh to comment on whether variability among pericardial thickness measurements might appear to be high because the observed values fall into a relatively small range. Dr. Oh and a panelist indicated that the range of pericardial thicknesses in the Vieques Heart Study is less than the ranges of the other functional and structural parameters measured, although the variability in measurements of pericardial thickness (in relation to its absolute value) is greater. Dr. Oh added that all measurements made from the Doppler echocardiograms appeared to be highly precise, while measurements of pericardial thickness were not. He concluded that the variability in pericardial thickness measurement was much greater than that of measuring other cardiac dimension or hemodynamic parameters.

Concerned about the implications of the variability data, a panelist asked Dr. Oh if any systematic differences were observed between the primary sonographers' measurements. A participant shared this concern, wondering why the measures were highly precise for all parameters except pericardial thickness. In response, Dr. Oh showed the distributions of measurements of pericardial thickness made by himself and by the primary sonographers. The medians of the distributions for the nonmagnified readings were approximately 1.3 mm, 1.7 mm, and 1.7 mm. Dr. Oh indicated that an 0.4 mm difference in medians should not be viewed as a significant error, given that he did not think echocardiography can achieve a resolution finer than approximately 1.0 mm (see Section 2.1.4).

2.1.4 Limitations of Using Echocardiography to Measure Pericardial Thickness

Dr. Oh acknowledged that echocardiography has many advantages, but he noted that it has several limitations, including limited precision in measuring structures at sub-millimeter dimensions. Following are some of Dr. Oh's specific comments on the limitations of using echocardiography for the Vieques Heart Study:

Concerns about how image acquisition affects echocardiographic images. Dr. Oh was concerned that practices of the echocardiogram operator at the time of image acquisition might have influenced the quality of images acquired. For instance, he noted that inconsistent use of gain settings, particularly time-gain compensation (TGC), can affect subsequent measures of pericardial thickness—an issue the panelists revisited when discussing Question Area 2 (see Section 4.0). He added that the angle between the transducer and the chest wall might have varied from subject to subject, although he noted that the angle would have to change substantially before causing significant errors in measured pericardial thickness. Finally, a panelist asked if inconsistent placement of the transducer might bias results. Dr. Oh, however, was not very concerned about the placement, noting that all pericardial images were acquired from the posterior portion of the left ventricle.

Difficulties in reading images after acquisition. Dr. Oh noted that even if no systematic biases affected image acquisition,, measuring dimensions of fine cardiac structures from echocardiographic images is a complicated task. First, he explained how M-mode echocardiographic images clearly show that pericardial thickness varies throughout the cardiac cycle. Thus, even though PSM and Mayo Clinic investigators both measured the thickness at "end diastole," the thickness can vary even over short time frames that can reasonably be considered as end diastole. Second, Dr. Oh indicated that the pericardial thickness evident from an echocardiographic image can vary significantly across cardiac

cycles of an individual subject. His approach was to average the thicknesses observed in multiple cycles while rejecting any thicknesses that appear to be outliers. Third, Dr. Oh showed images for which sonographers had difficulty determining exactly where the leading edge of the pericardium begins and where the trailing edge ends. Overall, the Mayo Clinic investigators rejected 29 images due to difficulty in measuring the pericardium thickness, primarily due to blurring of the pericardial image at end diastole or overlap of the pericardial image with other structures (e.g., posterior wall)[**]. But even for the images of sufficient quality to read, Dr. Oh had concerns about the precision of the measured pericardial thickness, as Section 2.1.4 describes in greater detail.

S*cientific literature on how accurately echocardiographic images portray pericardial thickness*. Dr. Oh referred to results from the only scientific publication he knew of comparing echocardiographic measurements of pericardial thickness in laboratory animals against actual anatomical thicknesses measured after the animals were sacrificed. The study found that pericardial thicknesses measured from echocardiographic images were consistently greater than the actual thicknesses, and that echocardiographic measurements and actual measurements were not strongly correlated ($R^2 = 0.34$). Dr. Oh noted that this study also showed that changes to the gain settings in the ultrasound caused the dimensions of the pericardia to appear larger than they actually are[6].

Given these concerns, Dr. Oh said that he would not have recommended using transthoracic echocardiography to determine sub-millimeter differences in pericardial thickness. Transesophageal echocardiography and other imaging techniques (e.g., computed tomography) are known to achieve finer resolution. As discussed later in the report, however, the PSM investigators did not intend to use echocardiography to detect sub-millimeter differences in

[**] Dr. Oh noted that 7 images were rejected because they were not accompanied by EKGs. Some of these were among the 29 images rejected due to difficulties measuring pericardial thickness. Additionally, citing exclusion statistics for other research projects, Dr. Oh noted that the 30% of echocardiographic measurements that Mayo Clinic excluded from the Vieques Heart Study should not be viewed as an unusually high rejection rate.

pericardial thickness: the goal of the Vieques Heart Study was to determine whether the pericardia among Vieques fishermen was more than 1 mm thicker than those of a comparison population (see Section 4.3).

2.2 Summary of Presentation by Dr. Ríos, Ponce School of Medicine

Dr. Ríos summarized various aspects of the Fishermen Cardiovascular Study (referred to in this report as the Vieques Heart Study), focusing primarily on the study methods and results. Dr. Ríos first identified the investigators who contributed to the study, then indicated the study objective: "to determine the occurrence of an association between place of residence and the presence of morphological cardiovascular changes among fishermen." To meet this objective, the team of investigators designed and implemented a cross-sectional epidemiological study, the details of which are reviewed in the following sections.

2.2.1 Methods Used for the Vieques Heart Study

Dr. Ríos described the methodology used to implement the Vieques Heart Study. First, the researchers attempted to recruit 80 commercial fishermen from Vieques and another 80 from Ponce de Playa (Ponce) to participate in the study. The investigators' power calculations indicated that this total number of subjects (160) was necessary to detect an average pericardium size difference of 0.5 mm. Details on recruiting subjects follow:

- *Vieques fishermen*. The registry of licensed fishermen in Vieques was the sampling frame. The investigators randomly selected and subsequently contacted 80 individuals from this registry. Of these 80 individuals, 2 were deceased, 10 no longer lived in Vieques, and 16 refused to participate in the study, leaving a sample size of 53 Vieques fishermen (because of overlap among excluded groups). No efforts were made to characterize non-participants.

- *Ponce fishermen*. Because the registry of commercial fishermen in Ponce included 52 individuals, the PSM investigators attempted to recruit all fishermen in the registry, not a subset of the individuals. Of the individuals in the registry, the PSM investigators recruited 43 to participate in the study.

All 96 subjects were then asked to complete a questionnaire. The questionnaire addressed basic demographic information (e.g., age and place of residence) and numerous questions concerning potential confounding factors. These confounding factors included previous diagnosis of conditions or diseases that might be associated with pericardial thickening, as identified by cardiologists on the research team. Such diseases and conditions include tuberculosis, high blood pressure, scleroderma, lupus, diabetes, and others. All responses on these health status variables were self-reported. One panelist asked Dr. Ríos about potential biases associated with using self-reported morbidity data in communities known to have very limited access to health care, such as Vieques (see Section 1.3). This panelist was particularly concerned that Vieques residents might not be aware of confounding diseases or health conditions, because they might never have been diagnosed. Dr. Ríos acknowledged that such biases, if any, are impossible to characterize, although he expressed confidence that subjects provided accurate responses regarding their health histories.

Dr. Ríos then reviewed details on how echocardiographic images were collected and analyzed. Echocardiographic examinations were conducted on all 96 subjects, and both groups of subjects were examined in the communities where they reside. One certified technician administered the examinations for all subjects. A group of cardiologists then met at Ponce to read the echocardiographic images. The readers were blinded to information on the subjects (i.e., they did not know if a given image was for a subject from Ponce or from Vieques). All readings were done by consensus among the observers; no repeated measures were obtained to characterize reproducibility.

When responding to panelists' questions, Dr. Ríos and other PSM investigators provided additional information on the study methods. For example, the study did not include any measures of exposure to noise, because the study objective was simply to identify differences between the groups in cardiac structure, without attributing them to any factor other than location of residence. Dr. Martínez Maldonado clarified that the Vieques Heart Study considered fishermen because they are believed to be the subset of Vieques residents most exposed to noise during the Navy exercises. Fishermen, he said, are consistently closer to the Navy ships than any other subset of Vieques residents.

2.2.2 Preliminary Results of the Vieques Heart Study

Dr. Ríos presented findings from the questionnaires and the echocardiographic readings. First, he noted that the average age of the Vieques subjects (N = 53) was 45, while the average age of the Ponce subjects (N = 43) was 55, and that this age difference was statistically significant. He added that both study groups were very similar in terms of the health conditions reported on the questionnaires: some slight differences were observed between the groups, but none was statistically significant. The groups also were similar in terms of highest level of education received. Dr. Ríos argued that this parameter is probably the best reflection of socioeconomic status for the study groups. Dr. Ríos added that no statistically significant differences existed between the populations in several other parameters, including smoking status, height, and weight. He then emphasized that the only statistically significant difference between the populations was average age.

Next, Dr. Ríos presented the main finding from PSM's reading of the echocardiographic images: the pericardia of Vieques fishermen were, on average, thicker than those of Ponce fishermen; and the "aortic valve thickness" among Vieques fishermen was greater than that among the control

group[***]. Both differences in average thickness were statistically significant. Dr. Ríos indicated that these statistically significant differences remained even after the investigators adjusted for age. Statistical analyses were not performed to test whether other variables (e.g., smoking history) are confounding factors. Table 2-1 presents the preliminary data, and compares the results generated by the PSM investigators with those generated by the Mayo Clinic investigators. Section 2.2.3 discusses the measurements of pericardial thickness in greater detail.

Finally, Dr. Martínez Maldonado presented data on measurements other than pericardial thickness made from the echocardiographic images. He first displayed average measurements for the following parameters: left ventricle outflow tract velocity, height of the E-wave, height of the A-wave, left ventricle outflow tract diameter, end-diastolic volume of left ventricle, and others. For all of these parameters, Dr. Martínez Maldonado stated that the average readings generated by the Mayo Clinic were not considerably different from those generated by the PSM investigators, and no differences were statistically significant. Moreover, for this list of parameters, his data indicated that the average readings for the Vieques subjects (as determined by either team of investigators) were not significantly different from those for the Ponce subjects. For end-systolic volume of left ventricle, however, the measurements by the two teams of investigators differed, on average, by approximately 45%. When discussing this difference further, PSM investigators indicated that they used the Simpson method to measure the end-systolic volume of the left ventricle, while the Mayo Clinic investigators used the bullet method. Several participants opined that the difference in the measurement of end-systolic volume was consistent with the fact that the two groups used different methods to measure this variable.

[***] A participant later clarified that the Vieques Heart Study did not find the aortic valve thickness to differ between the two study groups. Rather, the aortic valve opening was greater among the Vieques fishermen than the Ponce fishermen. One panelist questioned the significance of aortic valve opening, noting that more relevant observations would be aortic valve leaflet thickening or restrictions in opening. Further, when data on this parameter were presented later in the meeting, another panelist noted that the apparent difference in aortic valve opening (or aperture) exists in the echocardiographic measurements made by PSM investigators, but not in those made by the Mayo Clinic investigators. No further information was provided on this issue.

2.2.3 Questions and Answers

After reviewing the methods and results of the Vieques Heart Study, Dr. Ríos and the other PSM investigators responded to the panelists' and participants' questions, as summarized below:

Comments on sample sizes for the Mayo Clinic and PSM data. After Dr. Ríos presented the data shown in Table 2-1, panelists asked Dr. Ríos and the PSM investigators whether the difference in the results (that is, a statistically significant difference between groups in pericardial thickness using PSM measurements but not Mayo measurements) might arise from the two research teams having different sets of images. (The Mayo investigators had rejected some images for pericardial measurement. These were not precisely the same images as had been rejected by the PSM investigators.) Dr. Ríos noted that sample sizes were different because the Mayo Clinic investigators rejected more echocardiographic images than did the PSM investigators. The panelists asked the PSM investigators to present paired comparisons of the pericardial thickness measurements for those subjects for whom a pericardial measurement was made by both teams of investigators. This comparison was displayed later in the meeting (see Section 3).

Multivariate statistical analyses. Two panelists asked whether PSM investigators conducted multivariate statistical analyses to investigate potential confounders. Dr. Ríos responded that their statistical methodology was to consider only those factors with a statistically significant difference ($p < 0.05$) between the study and control populations as potential confounders. Because age was the only parameter found to have statistically significant differences between the populations, Dr. Ríos indicated that PSM investigators controlled only for age when analyzing data on pericardial thickness, but they did not do so for any other variable. Later in the meeting, Dr. Ríos presented summary statistics for various characteristics of the study populations, such as age, weight, smoking history, and a recollection of being diagnosed with certain diseases.

Measurements of pericardial thickness from unmagnified views. After viewing the data on pericardial thickness measurements made from magnified views (see Table 2-1), one participant asked if a similar comparison could be made between pericardial thickness measurements made from unmagnified views. Dr. Martínez Maldonado responded that such a comparison is not possible, because the PSM investigators measured pericardial thickness using only magnified views.

Clinical significance of findings. Some panelists began to discuss the clinical significance of pericardial thickening during the question and answer session—an issue the panelists discussed in greater detail when responding to Question Area 2 (see Section 4). During this discussion, Dr. Ríos clarified that the purpose of the Vieques Heart Study was to determine whether a group of Vieques fishermen had thicker pericardia than a comparison group from Ponce. He added that addressing clinical significance of thicker pericardia would be a logical follow-up research project, if such an outcome were observed.

Measurements other than pericardial thickness. Although the primary objective of the Vieques Health Study was to characterize pericardial thickness among the two study populations, one participant thought the available data allow for more detailed analyses of ventricular function (including its age-dependence) and the dimensions of other heart structures. He advocated conducting these additional analyses both because they are conventionally measured using echocardiography and because they have much greater clinical relevance than sub-millimeter increases in pericardial thickness. In short, this participant advocated expanding the data analysis beyond the original objectives of the Vieques Heart Study. The PSM investigators commented on this issue later in the meeting (see Sections 4.5 and 5).

Other comments. One panelist asked the panel to comment on what, if anything, is known

about the age-dependence of pericardial thickness in the overall population, given that age was apparently the main difference between the study and control populations. No panelists or participants responded. Finally, another panelist recommended, and other panelists agreed, that the two teams of investigators collaborate on a publication on inter-institutional variability in echocardiographic measurements of pericardial thickness.

Table 2-1
Average Pericardial Thicknesses Based on Echocardiographic Readings Conducted by PSM and by Mayo Clinic

Parameter	PSM Results	Mayo Clinic Results
Total number of recordings	84	69
Observations for Vieques fishermen		
Average thickness	1.20 mm	0.78 mm
Standard deviation	0.23 mm	0.15 mm
Standard error	0.04 mm	0.02 mm
Observations for Ponce fishermen		
Average thickness	1.05 mm	0.82 mm
Standard deviation	0.24 mm	0.14 mm
Standard error	0.04 mm	0.002 mm

Notes: Data presented by Dr. Ríos.
Data in this table are thicknesses determined from magnified views of echocardiographic images.
The two groups of investigators used different exclusion criteria, resulting in different numbers of subjects in the between-group comparisons. Out of the 95 echocardiographic images collected, PSM investigators rejected 11 for measuring pericardial thickness and the Mayo investigators rejected 29. Refer to Table 4-1 for a paired comparison between the two investigators.
The PSM results showed that the pericardia among the Vieques fishermen studied, on average, were thicker than those of the Ponce fishermen studied—a statistically significant difference. The Mayo Clinic results found the opposite trend, but the difference in their findings was not statistically significant.

3.0 COMMENTS ON STUDY DESIGN AND DATA ASCERTAINMENT

Question Area 1 in the charge to the reviewers (see Appendix C) addressed the design of the Vieques Heart Study and data ascertainment. The charge question asked: "How effectively does the study design minimize the possibility that bias or confounding explain any of the observed associations? Please consider the following issues in your answer:

- Identification and comparability of sampling frames
- Sampling (of exposed and control persons)
- Non-response and measures taken to deal with it
- Ascertainment of non-echocardiographic information related to exposed persons and controls
- Availability of data on potential confounders"

Discussions on this question area opened with the PSM investigators presenting some information on study design not mentioned in their opening presentation (see Section 2.2). A PSM investigator explained that the sampling frame was intended to be 80 fishermen from Vieques and 80 fishermen from Ponce. Subjects were selected from the fishing registries for the two locations. Because the fishing registry at Vieques included more than 80 individuals, the PSM investigators randomly selected a subset of 80 as the sampling frame. The fishing registry at Ponce included 52 individuals, all of whom were considered as the sampling frame. The PSM investigators noted that the two communities have licensing requirements for all commercial fishermen, thus ensuring that the registries themselves do not include a non-random subset of the overall fishing population.

Regarding comparability of the populations, the PSM investigators noted that the only statistically significant difference between the study and control groups was age (the Ponce population being 10 years older, on average, than the Vieques population). The information

collected on medical status and other demographic data revealed no statistically significant differences between the two groups. Medical status information included blood pressure, alcohol usage, and past diagnoses of diseases known or suspected to be associated with pericardial thickening (e.g., diabetes, lupus, scleroderma, tuberculosis).

The subsequent discussions focused on various aspects of Question Area 1, and are summarized below in five main categories:

Response rates. The panelists asked the PSM investigators to present additional detailed data on sampling frames and response rates. A PSM investigator cited a series of relevant data on this matter, summarized in Table 3-1. The data indicated that, on average, nearly 80% of the individuals in the selected sampling frame agreed to participate in the Vieques Heart Study.

Referring back to the summary statistics presented earlier (see Table 2-1), a panelist asked why the number of individuals who agreed to participate in the study (96; see Table 3-1) exceeded the number of recordings considered when calculating pericardial thickness (84; see Table 2-1). The PSM investigators explained that some echocardiographic images were rejected from the analysis because they did not have corresponding EKG data, which are needed to ensure that all readings take place at the same point in the cardiac cycle. Some discussion followed on whether response rates should be calculated as the number of valid images obtained divided by the sampling frame or as the number of individuals who agreed to participate divided by the number of eligible participants. No resolution was reached on this matter.

The data on response rate triggered two additional concerns. First, two panelists wondered why a considerably larger proportion of echocardiographic images collected on Vieques were rejected for measurement of pericardial thickness than those collected on

Ponce (see Table 3-1). Given the unlikely possibility that this difference resulted merely from chance, the two panelists thought the different proportion of rejected images suggested that the technician who administered the examinations might not have done so in an identical fashion in the two study populations. The panelists revisited this issue when discussing Question Area 2 (see Section 4). Second, a participant wondered if the Vieques Heart Study might lack statistical power, given that the power calculations supported the use of 160 total subjects and only 85 valid echocardiographic images were collected. The PSM investigators noted that their power calculations were very conservative and their sample size was adequate to detect the differences in pericardial thickness (i.e., greater than 3 mm) reported in the pilot study.[3]

Issues of non-response. The panelists discussed three issues pertaining to non-response and the PSM investigators' attempts to deal with it. First, several panelists and participants asked the PSM investigators if they made attempts to characterize the non-respondents, possibly through a questionnaire. The PSM investigators indicated that their study, as approved by the Institutional Review Board (IRB) did not include any provision for such follow-up activities. As a result, they were not authorized to ask any questions of individuals who did not sign informed consent forms. Given the importance of ensuring that non-respondents account for a random subset of the sampling frame, several panelists and participants recommended that the PSM investigators request permission from the IRB to conduct a brief questionnaire study of non-participants.

Second, the panelists had some concerns regarding the use of compensation to recruit subjects. When asked about measures to increase response, the PSM investigators indicated that they paid a subset of the Ponce fishermen $15 each to increase response rates among the control group, while no such efforts were made to increase response rates among the Vieques fishermen. One panelist commented that, with this approach, the subjects in the study had different motivations to participate—a fact that could lead to

bias in the results. Others agreed, noting that compensating study participants is standard practice in many epidemiological studies and clinical trials, but compensating only a subset of the study participants is not. These panelists indicated, however, that the PSM investigators can assess the potential bias associated with the compensation practices by comparing the average pericardial thickness among the Ponce fishermen who were compensated to that among the Ponce fishermen who were not.

Finally, noting that the final number of subjects with valid echocardiographic images (85) was roughly half the number of subjects identified in the power calculations (160), a participant wondered why the PSM investigators did not attempt to identify and recruit additional subjects, perhaps including those not in the fishing registries. A panelist responded that the approach of limiting the sampling frame to fishermen is appropriate, given that an underlying hypothesis in the study is that exposure to noise from Navy bombing exercises causes pericardial thickening and that Vieques fishermen (as opposed to other island residents) are believed to be the population most exposed to this noise.

*Data on potential confounders*. Before the panelists discussed potential confounders, the PSM investigators explained their approach to identify and characterize such variables. After consulting with several physicians, the investigators developed a list of potential confounders, including various illnesses (e.g., lupus, scleroderma, kidney disease, diabetes, tuberculosis) and other indicators of health status (e.g., smoking history, alcohol usage, blood pressure, frequency of chest pain). The PSM investigators commented that the two study populations had no statistically significant differences in any of the potential confounding factors, except for a significant difference observed in the average age of the study populations. The PSM investigators added that all participants were given physical examinations, during which certain potential confounding factors were measured (e.g., blood pressure) and others related to medical history and co-morbid factors were discussed.

The panelists had two general concerns about the potential confounding factors. First, regarding the potential confounders identified by PSM investigators, a panelist wondered how accurate self-reported morbidity data are for the study populations, which reportedly have limited access to medical care. The PSM investigators shared this concern, but doubted that the morbidities considered as potential confounders (e.g., lupus, scleroderma) would be undetected—both historically for a given subject and during the provided physical examinations. A participant agreed, noting that Puerto Rico has active surveillance systems for tuberculosis and that the likely study populations do access medical care for more serious morbidities, such as lupus.

Second, the panelists wondered if confounders other than those identified by the PSM investigators might bias results. For example, two panelists and a participant commented that pericarditis is associated with conditions that are not readily diagnosed, particularly viral infections. One panelist referred to studies from the 1960s to more recently in which electrocardiographic and clinical evidence of pericarditis were found in individuals with a variety of viral infections. The mild myopericarditis usually resolved over time.[7,8,9,10,11,12] Referring to the findings of one of his own studies, a participant indicated that the second most common cause of constrictive pericarditis among a sample population was believed to be viral infection, and that many subjects in the study were completely unaware of these infections.[13] Commenting on these concerns, an ATSDR scientist said that some infections that might cause pericardial thickening (e.g., coxsackievirus infections) are difficult to detect, especially among populations with limited access to medical care. In short, these comments suggested that the Vieques Heart Study might not have considered all possible confounding factors for pericardial thickening, although in any event, confounding by viral infection would have been difficult to ascertain.

In response, a PSM investigator doubted that a widespread pericarditis-causing viral

infection (e.g., coxsackievirus) could have gone undetected among either study group. A panelist added that gathering information on past viral infections is extremely difficult and he doubted whether an alternate study design would have been more effective at identifying past exposures to pericarditis-causing viral infections.

Comparability of study and control groups. When comparing Vieques and Ponce fishermen, the panelists and participants first recounted comments made during the opening presentations (see Section 1.3). For instance, a panelist recalled that the Vieques population has to travel to the main island of Puerto Rico for most types of health care beyond general practice; and one of the co-chairs noted that the demographic data suggest that the population of Vieques is poorer than that of Puerto Rico as a whole. Following these observations, a panelist recounted several ways in which the two study populations differ:

- The Vieques population was not compensated for participating in the study.
- The Vieques population, on average, was younger than the Ponce population.
- The Vieques population does not have as immediate access to health care as the Ponce population and might therefore be less likely to have underlying pathologies diagnosed.
- The quality of the echocardiographic readings, as determined by the proportion of rejected images, differs between the two populations.

Given these differences, the panelist wondered if the relatively small difference observed in pericardial thickness, as determined by the PSM investigators, might simply reflect the populations' dissimilarities. The panelists discussed in detail issues of measurement when

they addressed Question Area 2 (see Section 4).

Other issues. The panelists and participants raised the following additional questions about study design, but these were not discussed in great detail. First, a CDC scientist was concerned that individuals who were identified in the pilot study as having thickened pericardia might be more likely to participate in the Vieques Heart Study. The PSM investigators indicated that they did not ask about participation in past studies when recruiting subjects for the Vieques Heart Study. Second, a participant asked if the PSM investigators considered infection with the human immunodeficiency virus as a potential confounder. The PSM investigators indicated that they did not. Third, a panelist asked if the PSM investigators collected any data characterizing subjects' exposures to noise. The PSM investigators acknowledged the utility of such data, but added that the purpose of the study was merely to examine statistical differences in pericardial thickness without attributing observed differences to any specific cause. Finally, after hearing that a considerable portion of the Vieques fishermen might actually come from just two large families, an ATSDR scientist asked the panelists to comment on the possibility of pericardial thickening having genetic causes. Other than one participant's anecdotal account of a family with several members having constrictive pericarditis, no panelists or participants commented on this issue.

Table 3-1
Data on Response Rates and Collection of Echocardiographic Images

Parameter	Ponce Fishermen	Vieques Fishermen
Sampling frame	52	80
Eligible participants	52	69 (*)
Final number of participants	43	53
Response rate (†)	83 %	77 %
Number of echocardiographic exams given	43	53
Number of valid images collected (‡)	42	43
Percent of exams generating valid images	98 %	81 %

Notes: Data presented by Dr. Ríos:

(*) The number of eligible participants in Vieques is lower than the sampling frame because several individuals in the Vieques fishing registry had either died or moved off the island.

(†) Response rate here is defined as the fraction of eligible participants who agreed to participate in the Vieques Heart Study.

(‡) For this display, a "valid image" is considered an echocardiographic image with a corresponding electrocardiogram. Both are needed to ensure that readers measure pericardial thickness at the same point in the cardiac cycle. Note, however, that readers from both PSM and the Mayo Clinic rejected some of these "valid images" for other reasons.

4.0 COMMENTS ON ECHOCARDIOGRAPHIC MEASUREMENTS

The panelists and participants discussed Question Area 2—echocardiographic measurements—at length, not only during the meeting time designated for Question Area 2, but also during discussions on the other question areas. This section reviews all of these discussions, regardless of when they took place. For reference, the exact text of Question Area 2 reads:

"Please comment on the echocardiographic measurements made, addressing (if relevant) the following issues:

- Sensitivity, specificity, and reproducibility
- Mechanical (machine-based) and human variability
- Blinding
- Interobserver and intraobserver variability of measurements
- Clinical significance of abnormalities noted"

The panelists and participants discussed these issues extensively. The following five subsections summarize the discussions on four specific categories: collection of echocardiographic images (Section 4.1), reading the images (Section 4.2), limitations of echocardiography (Section 4.3), differences between the PSM and Mayo Clinic readings (Section 4.4), and clinical significance of the reported findings (Section 4.5).

4.1 Comments on How Images Were Collected

The PSM investigators provided background information on the procedures followed to collect the echocardiographic images. One trained, experienced technician collected all images, using one echocardiogram machine, and never adjusting the transducer frequency or the compression settings. The technician did, however, adjust the TGC differently for the individual subjects, and

these variable settings were not recorded. (Panelists noted that it was also necessary to change the overall gain between examinations because of between-subject differences in chest wall characteristics.) The images were collected at two locations—one on Vieques and one in Ponce—but in examination rooms that had similar set-ups. No one supervised the performance of the technician during image acquisition.

The panelists' comments on the echocardiographic examinations addressed the following two principal issues:

Potential biases associated with performing echocardiographic examinations. The panelists discussed several potential biases that might be associated with the procedures the PSM investigators followed to collect echocardiographic images. The fact that the technician who collected the images was not blinded to the study and control groups was of particular concern. Specifically, a panelist indicated that the technician might have been more likely to follow slightly different procedures when conducting examinations at Vieques as opposed to at Ponce, especially considering the publicity surrounding the Navy bombing and the preliminary data suggesting pericardial thickening among Vieques residents. In short, the panelist was concerned that a slight, systematic bias might have affected image acquisition because the technician was not blinded to the two study populations.

A PSM investigator doubted that such a bias could have occurred given the tight schedule followed for acquiring images. The technician, the investigator suspected, would not have had enough time to adjust settings selectively and complete all echocardiographic examinations within the allotted time. Moreover, he felt that that the study would likely have found a much greater magnitude of pericardial thickening if such a systematic bias truly occurred.

A panelist disagreed with this argument, citing examples of how well-intentioned field workers have unintentionally introduced systematic biases into past studies. Because the differences in pericardial thickness observed by the PSM investigators was relatively small, this panelist wondered if a slight, unintentional bias might account for the main result. A cardiologist on the panel agreed that use of inconsistent practices when conducting echocardiographic examinations can result in slight changes in results, such as the 0.15 mm difference in pericardial thickness reported in the Vieques Heart Study. These panelists acknowledged, however, that systematic biases introduced by the technician, if any, are impossible to quantify from the existing data.

To support his concern about the practices followed when collecting images, a panelist referred to the data on the percentage of echocardiographic images rejected because they did not include a corresponding EKG (see Table 3-1). The data indicate that 19% of the echocardiographic images taken at Vieques were rejected for this reason, as compared to only 2% of the readings from Ponce. In other words, these rejection rate data do not appear to be randomly split between the groups, as one would expect if the technician consistently applied uniform techniques when acquiring images.

*Concerns about inconsistent use of TGC settings*. A specific concern about the technician's practices was the apparent use of different TGC settings from one subject to the next. A panelist indicated that TGC settings affect the intensity of echocardiographic signals, and increasing the setting generally makes cardiac structures appear thicker than they actually are. Another panelist and a participant agreed, citing their experiences of how altering TGC settings can change the apparent dimensions of materials, whether heart structures or test films over lucite blocks. A participant noted that an article in the scientific literature also documents how gain settings on echocardiograms can blur output signals and therefore artificially increase the apparent thickness of heart structures.[6] On the other hand, a consultant to the PSM investigators commented that TGC settings

> actually have little impact on measuring pericardial thickness, because slight changes to the settings cause the pericardium either to vanish from an image altogether or to expand to unrealistically large dimensions—both outcomes, he argued, would be easily identifiable as artifacts by those reading the images.

Following this discussion, some panelists raised concerns that subtle changes in the technician's procedures for acquiring echocardiographic images might account for the very small between-group differences in pericardial thicknesses reported in the Vieques Heart Study. A participant indicated that the only way to verify this concern is to have another research team collect echocardiographic images from the same individuals considered in the Vieques Heart Study and compare the results to those generated by the PSM investigators. As Section 6 notes, however, most panelists eventually agreed that follow-up studies of pericardial thickening are not needed.

4.2 Comments on How Images Were Read

As Section 2 notes, the PSM investigators read all echocardiographic images collected during the Vieques Heart Study. At the request of ATSDR and PSM, investigators from the Mayo Clinic then performed independent readings of the same data. Both teams of investigators measured pericardial thickness at end-diastole, and both teams measured several additional parameters (e.g., left ventricular volume) from the echocardiographic images. Despite these similarities, the main finding from the PSM investigators—that pericardia among Vieques fishermen, on average, were thicker than those among Ponce fishermen—was not reproduced when the measurements made by the Mayo Clinic investigators were used in the analysis.

The panelists considered how practices used to read the echocardiographic images might have led to a measurement bias, and hence the differing conclusions. They highlighted three key points:

Inherent difficulties reading pericardial thickness from M-mode images. A participant and two cardiologists on the panel listed several difficulties associated with using M-mode echocardiographic images to measure heart structures on sub-millimeter scales. The participant, for example, displayed a typical M-mode image from the Vieques Heart Study and indicated how the signal for the pericardial thickness varied, even over the range of the cardiac cycle that can be considered end diastole.This variation, he argued, can lead to two sonographers reporting different pericardial thicknesses for the same echocardiographic image. A panelist agreed, adding that even the orientation of the viewer with respect to the screen can cause notable differences in echocardiographic data. Specifically, an individual looking down on a computer screen would probably read a greater pericardial thickness than one sitting in front of the computer screen. Finally, a panelist stated that echocardiographic images often have discontinuous lines and other artifacts in the M-mode signal, thus complicating efforts to discern "noise" from where a heart structure actually begins or ends. In fact, for this very reason inexperienced sonographers commonly overestimate the thickness of heart structures (e.g., the left ventricular wall). These panelists wondered if such subtle differences in techniques for reading the echocardiographic images could account for the differences observed between the PSM readings and the Mayo Clinic readings, as Section 4.4 discusses in greater detail.

Use of different approaches to make the measurements. During this discussion, the panelists commented on the slightly different approaches used by the PSM and Mayo Clinic investigators to read the echocardiographic images. At PSM, a group of physicians came to a consensus reading on every image. At the Mayo Clinic, on the other hand, the images were assigned to two experienced sonographers and each image had a designated primary sonographer. The reading from the primary sonographer was considered "final," except in cases where the two readings had noteable discrepancies. In these cases, which were few in number, the reading from an independent observer (Dr. Oh) was used.

Two panelists weighed the advantages and disadvantages of these approaches, but eventually agreed that both approaches are reasonably valid. One of these panelists did not think the differences between the PSM and Mayo Clinic readings could be explained by the approaches used by the two teams; a more likely explanation of the results is that the differences observed between the PSM and Mayo Clinic measurements fall within the commonly accepted resolution of echocardiography. Section 4.3 revisits this issue.

Other concerns. The panelists raised two additional concerns when discussing how the two teams of investigators read the echocardiographic images. First, referring to the data in Table 2-1, one panelist noted that the PSM investigators successfully read 84 images, while the Mayo Clinic investigators successfully read only 69. The Mayo Clinic principal investigator explained that his sonographers rejected numerous images due to poor quality. The panelist wondered if the fact that the two teams of investigators considered different sample subsets might explain the discrepancy between their findings. However, data presented on paired comparisons (see Section 4.4) indicated that the difference between the PSM and Mayo Clinic findings remains and is of approximately the same magnitude, even if one considers only the subset of echocardiographic images successfully read by both groups. Second, one panelist noted that the Mayo Clinic sonographers, who reportedly knew that a “normal” pericardial thickness was less than 1.0 mm, might have been biased to read thickness in this range. This panelist acknowledged that this type of measurement bias, if it existed, would have applied to all readings, and not just those of the Vieques or Ponce fishermen. No other panelists or participants commented on this issue.

In summary, the panelists listed several inherent difficulties associated with measuring pericardial thickness from M-mode echocardiographic images. This discussion generated more detailed discussion on inherent limitations of echocardiography (see Section 4.3) as well as on the exact nature of the differences between the PSM and Mayo Clinic measurements (see Section

4.4).

4.3 Comments on Limitations of Echocardiography (Resolution)

Much of the panelists' discussion addressed the inherent limitations of echocardiography and whether this technique is capable of resolving differences in pericardial thickness on the order of 0.15 mm. The cardiologists on the panel unanimously agreed that echocardiography is a powerful and well-established tool for many applications, particularly for characterizing hemodynamics and the dimensions of certain heart structures. Several panelists and participants doubted, however, that echocardiography can reasonably and consistently measure sub-millimeter differences in a relatively thin cardiac structure such as the pericardium. These panelists acknowledged that echocardiography can detect gross differences in pericardial thickness, like those reported in the pilot study[3] that led to the Vieques Heart Study. Accordingly, most thought that use of echocardiography in the Vieques Heart Study was appropriate.

The panelists made numerous notable comments on the inherent limitations of echocardiography, which are grouped here into the following three topics:

Resolution of echocardiographic measurements. Many panelists thought the commonly accepted resolution of echocardiography is a critical issue when one interprets the reported 0.15 mm difference, on average, between pericardia among Vieques fishermen and those among Ponce fishermen. A CDC scientist explained that resolution is an intrinsic property of an instrument; echocardiography has a widely accepted resolution of 1 millimeter, so it cannot distinguish two points separated by this distance. A panelist added that echocardiography, in theory, cannot distinguish two films or layers less than the instrument's resolution. A PSM investigator questioned, however, if cardiologists agree that the minimum resolution of echocardiography is truly one millimeter; that is, most cardiologists could use echocardiography to differentiate pericardia 2 mm thick

from those 3 mm thick. The panelists did not respond to this comment. Regardless of the actual resolution of transthoracic echocardiography, however, several cardiologists on the panel agreed that this type of echocardiography is not capable of detecting a 0.15 mm difference in the thickness of the pericardium.

Another panelist added that devices known to have a resolution of approximately 1 millimeter do not necessarily yield measurements reproducible at that level. In the case of echocardiography, for instance, the resolution is strictly a property of the instrument. Numerous human factors, however, can cause echocardiographic measurements to have poor reproducibility, even when measuring structures thicker than 1.0 mm. A participant agreed, referring back to the panelists' previous discussions on the inherent difficulties—and potential biases—associated with both acquiring the echocardiographic images in the field and reading the acquired images in the laboratory.

Relative performance of other imaging techniques. After reviewing the inherent limitations of echocardiography for measuring pericardial thickness, the panelists briefly discussed the utility of other imaging techniques, particularly computed tomography (CT) and magnetic resonance (MR) imaging. A panelist noted that studies have shown that echocardiographic measures routinely overstate dimensions of heart structures, in comparison to actual anatomic dimensions measured during autopsy. A participant agreed and added that the variability associated with measuring other heart structures, such as left ventricular volume, is considerably greater for echocardiographic measurements than for either CT or MR imaging measurements. Based on these observations, the participant questioned the validity of using transthoracic echocardiography for deriving valid, reproducible measurements of pericardial thickness. This comment led to a debate on whether a "gold standard" exists for this measurement, as summarized below.

The "gold standard" for measuring pericardial thickness. After debating the benefits of

echocardiographic, MR, and CT imaging, the meeting co-chairs asked the panelists to comment on whether a gold standard exists for measuring pericardial thickness. The panelists agreed that no one device has been widely used for measuring pericardial thickness, largely because this type of measurement is not routinely made in echocardiography when one evaluates cardiac function. Rather, echocardiographers measure hemodynamic and other parameters, which they then use to characterize systolic and diastolic function.

So although no real gold standard exists, said several panelists and participants, both CT and MR imaging are likely the closest to a gold standard, given these techniques' superior capability to measure heart structures. A CDC scientist explained that the superior resolution of CT and MR imaging suggests their measurements are more likely to be reproducible if the same population is studied twice, as compared to the relatively poor reproducibility observed in the echocardiographic measurements made during the Vieques Heart Study (see Section 4.4). A panelist agreed and added that echocardiographic readings can be easily biased, even unintentionally, by field collection practices as well as by approaches to reading images. This panelist noted that CT and MR imaging produce images of almost the entire pericardium, leading to much more standardized readings. Finally, noting the advantages of CT and MR imaging, a panelist and a participant said they would recommend use of one of these techniques if the Vieques Heart Study were to be conducted again. As Section 6 indicates, however, most panelists did not think the issue of potential pericardial thickening in Vieques fishermen warranted further study.

Based on these discussions, the panelists and most participants agreed that echocardiography is a "sub-optimal tool" for measuring pericardial thickness at the dimensions of interest in the Vieques Heart Study. The fact that two experienced laboratories read the same set of images but obtained notably different results confirms this hypothesis. The next section addresses in greater

detail the reproducibility of measurements.

4.4 Comments on Differences Between the PSM and Mayo Clinic Data

After discussing their general concerns regarding echocardiographic measurements and potential biases associated with how images are collected and read, the panelists commented more specifically on differences between the PSM and Mayo Clinic readings of the Vieques Heart Study echocardiographic images. This discussion opened with the PSM investigators comparing their results to the Mayo Clinic results for the 66 subjects for whom both research groups successfully read echocardiograms (see Table 4-1).

The results (see Table 4-1) continue to show the same basic trend of the Vieques Heart Study results (see Table 2-1), even when considering this subset of subjects. Specifically, the data generated at PSM for these 66 subjects suggest that the pericardia of Vieques fishermen are, on average, 0.12 mm thicker than those of Ponce fishermen—a statistically significant difference (P value = 0.03). On the other hand, the Mayo Clinic data for the same subjects suggest that the pericardia of Ponce fishermen are, on average, thicker than those of Vieques fishermen, but this difference is not statistically significant (P value = 0.20). Noting the similarity between the data for the 66 subjects successfully read by both groups and the data for the overall pool of subjects (see Table 2-1), an ATSDR scientist commented that the difference between the PSM data and the Mayo Clinic data cannot be explained by the fact that the two groups rejected different numbers of echocardiographic images. Several panelists agreed.

After reviewing these data, the panelists debated the true nature of the differences between the PSM and Mayo Clinic measurements. The discussions focused on three topics:

- *Magnitude of differences between the PSM and Mayo Clinic data*. Referring to the data in Table 4-1, a panelist noted that the differences between the PSM and Mayo Clinic data

are relatively small. Specifically, for Vieques fishermen, the PSM and Mayo Clinic average readings differ by 0.38 mm; for Ponce fishermen, this difference is 0.21 mm. This panelist and a participant were encouraged by the fact that these differences fall within the generally accepted resolution of transthoracic echocardiography. The panelist added that the relatively high inter- and intra-observer variability observed by the Mayo Clinic suggests that the measurements were conducted in a range lower than can be resolved using echocardiography. Or, stated differently, the dimensions are so small that one would expect to see highly variable data due to random measurement errors (i.e., "noise"). The panelists revisited this issue when discussing the correlations between the PSM and Mayo Clinic data (see below).

When discussing the differences observed in pericardial thickness, a participant and some panelists noted that the PSM and Mayo Clinic measurements for all parameters other than pericardial thickness appeared to be in excellent agreement. They were encouraged by this similarity and suspected that the differences observed in measurements of pericardial thickness probably resulted from attempting to discern differences of magnitudes lower than commonly accepted echocardiography resolutions.

Inconsistencies in the differences between the PSM and Mayo Clinic data. Some panelists observed that the differences between the PSM and Mayo Clinic data were more pronounced for the Vieques subjects than for the Ponce subjects. Specifically, as Table 4-2 shows, the percent difference between the PSM measurements of 31 Vieques subjects and the Mayo Clinic measurements of the same subjects was 49%, while the PSM-Mayo Clinic percent difference for a group of 35 Ponce subjects was only 25%. Because both PSM and the Mayo Clinic were blinded to information on the subjects, the two panelists noted that they would expect the percent difference between the two measurements be similar for both the study and control groups. The data provided, however, suggest that the differences between the PSM and Mayo Clinic measurements were not randomly

distributed between the Vieques and Ponce echocardiographic images. Further discussion failed to elucidate the reason(s) for this finding.

One panelist offered a possible explanation for the trend shown in Table 4-2: the inconsistencies might reflect the use of an inadequate sample size to detect fine differences in pericardial thickness, especially in a range shown to have considerable variability among measurements. An ATSDR scientist and a panelist recommended that PSM further investigate the data to determine whether the inconsistencies shown in Table 4-2 can be explained by other factors, such as outliers or influential data points.

Correlation between the PSM and Mayo Clinic data. Given their concerns about the reproducibility of the pericardial thickness data, the panelists asked the PSM investigators to display a scatter plot showing paired comparisons of the measurements made by PSM and Mayo Clinic. A PSM investigator displayed this plot, which showed that PSM's pericardial thickness measurements were essentially uncorrelated ($R^2 = 0.046$) with the Mayo Clinic's measurements. According to two panelists, the correlation data shown indicate that the reproducibility of measuring pericardial thickness in the range of interest is extremely poor, calling into question the validity of using echocardiographic imaging for this application. A CDC scientist agreed, adding that the lack of reproducibility suggests that the differences in pericardial thickness observed in the Vieques Heart Study fall within echocardiography's range of measurement error.

Summarizing the group's discussion on the differences between the PSM and Mayo Clinic readings, one panelist observed that the pericardial thickness measurements were essentially not reproducible for the range of thicknesses noted. This lack of reproducibility suggests that the reported differences in pericardial thickness between the Vieques and Ponce fishermen likely fall within the range of the "noise" of measuring heart structure dimensions from echocardiography. Both these observations, he argued, are consistent with the cardiologists' claims that the

resolution of echocardiographic imaging is believed to be roughly 1.0 mm. Based on these arguments, the panelist concluded that the differences between the PSM and Mayo Clinic data are all within the range of random measurement error.

4.5 Comments on Clinical Significance

After reviewing the statistical significance of the pericardial thickness measurements, the panelists discussed the clinical significance of pericardial thickening and the echocardiographic measurements. This discussion was based strictly on the panelists' opinions on the available data. The PSM investigators had not published interpretations of the clinical significance of the Vieques Heart Study and expressed no opinion regarding clinical significance during the meeting. The panelists' comments on clinical significance addressed three general issues:

- *What is the thickness of a "normal" pericardium?* Although the panelists generally agreed that there is no consensus among cardiologists on exactly what pericardial thickness is considered "normal," they cited various figures on normal pericardial thickness from the scientific literature and other sources. For example, one panelist noted that the preliminary study of pericardial thickening reports a normal pericardial thickness of 1.5 mm for the population, as measured by echocardiography.[3] Further, a participant indicated that certain researchers consider pericardial thicknesses less than 2.0 mm as normal. Another panelist agreed, noting no known clinical relevance associated with pericardial thicknesses less than 2.0 mm. Finally, a PSM investigator suggested that normal pericardial thicknesses range from 0.5 to 1.0 mm, and thicker pericardia warrant further clinical investigation. Throughout this discussion, a participant cautioned that the figures cited might not be consistent because thicknesses of heart structures measured by imaging techniques often are not equal to the corresponding anatomical thicknesses.

On the second day of the meeting, a participant presented data on pericardial thickness he found in a literature search. This participant reviewed one article during the opening presentation (see Section 2.1); and now summarizes the abstracts from three other studies:

- A study of 18 healthy subjects using MR imaging found the average pericardial thickness to be 1.2 mm (± 0.5 mm) in diastole and 1.7 mm (± 0.5 mm) in systole. The resolution of MR imaging cited in the study was between 0.5 mm and 1.0 mm.[14]

- MR images taken from 23 subjects—17 "healthy" and 6 with "no known pericardial disease"—found an average pericardial thickness of 1.7 mm, but the study did not specify during which part of the cardiac cycle the measurements were made.[15]

- A CT imaging study of 100 healthy subjects reported that the thinnest part of the pericardium, on average, measured 1.2 mm based on 10 mm CT slices and 0.7 mm based on 1 mm CT slices.[16]

After reviewing these results, a panelist again noted that there is no universally accepted "normal" pericardial thickness for the general population, nor for the population of Puerto Rico.

*Clinical significance of the observed pericardial thicknesses*. The cardiologists discussed the clinical significance of two findings from the Vieques Heart Study. By PSM measurements, the pericardia of Vieques fishermen are, on average, 0.15 mm thicker than those of the Ponce fishermen. None of the subjects in the entire study, both from Vieques or Ponce, had pericardial thicknesses greater than 2.0 mm (a finding supported by both

the PSM and Mayo Clinic measurements).

When commenting on these figures, a panelist and a participant both remarked that cardiologists typically do not examine pericardial thickness as a pathology. Instead, they examine hemodynamics and markers of systolic and diastolic function to identify pathologies. The panelist and participant both noted that slight pericardial thickening (i.e., on the order of 0.15 mm) has no known clinical significance. In fact, the participant indicated that some patients with relatively thick pericardia on echocardiogram have been shown to have completely normal cardiac function. Furthermore, citing preliminary results from an unpublished study, this participant noted that even constrictive pericarditis has been shown to occur in the absence of any pericardial thickening. Based on these and other observations, two panelists and a participant agreed that the pericardial thickness measurements for the entire population of the Vieques Heart Study are within ranges typically observed in healthy individuals and have no known clinical significance.

*Use of the Vieques Heart Study echocardiograms for other measures*. Throughout the meeting, a participant recommended that the PSM investigators study further the Vieques Heart Study images to measure indicators more relevant to cardiac health (e.g., left ventricular mass, hemodynamic parameters). Moreover, noting the significant age difference between the two study populations, he recommended making age-adjusted comparisons for the parameters of interest. In short, he thought the PSM investigators could make better use of the available echocardiographic outputs by measuring for a broader suite of parameters.

Panelists agreed with this suggestion, but they added several caveats. Several panelists fully supported—in general—the use of echocardiography to measure the structural, functional, and hemodynamic parameters routinely evaluated with this instrument. Nevetheless, they cautioned the PSM investigators about the significance and quality of the data derived from these measures. First, a participant noted that measurements of

trans-mitral blood flow velocities were made at the level of the mitral annulus rather than at the more usual level of the mitral leaflet tips. This difference would complicate efforts to compare the data to those published in other studies. Second, a CDC scientist observed that the technician who conducted the echocardiographic examinations was not trained in Doppler imaging techniques, which raises questions about the validity of measurements made from the Doppler images. Third, noting that the power calculations for the Vieques Heart Study were based on detecting differences in pericardial thickness, two panelists were concerned that the existing data might not offer adequate power for detecting differences in other variables, particularly if age were an important covariate. They encouraged the PSM investigators to revisit their power calculations before evaluating the existing images further for other parameters. Finally, two panelists had more serious reservations about using the images to measure outcomes not considered in the original study design. They explained that, for example, examining various outcomes (e.g., variations in left ventricular mass) could require evaluating confounding factors not considered in the original study design.

Before concluding the discussion on clinical significance, panelists and participants briefly summarized the limited structural, functional, and hemodynamic data for the Vieques Heart Study subjects that the PSM investigators presented earlier in the meeting. For instance, one panelist and two participants stated that the data presented were not only consistent across the two study groups, but were also consistent between the PSM investigators and the Mayo Clinic investigators. Further, they thought all data presented were all within normal limits. A participant added that none of the echocardiographic data he reviewed suggested that any subjects had diastolic heart failure. The panelist and two participants thought these observations argue strongly against any underlying adverse cardiovascular effects among the two populations studied.

Table 4-1
Paired Comparisons of Pericardial Thickness Measurements by PSM Investigators and by Mayo Clinic Investigators

Parameter	PSM Investigators	Mayo Clinic Investigators
Data for the Vieques fishermen		
Number of "echos" read by both groups of investigators	31	31
Average pericardial thickness	1.16 mm	0.78 mm
Standard deviation	0.20 mm	0.15 mm
Standard error	0.04 mm	0.03 mm
Data for the Ponce fishermen		
Number of "echos" read by both groups of investigators	35	35
Average pericardial thickness	1.04 mm	0.83 mm
Standard deviation	0.24 mm	0.15 mm
Standard error	0.04 mm	0.03 mm
Statistical Significance of Differences Between Populations		
P Value	0.03	0.20

Notes: Data presented by Dr. Ríos:
Data in this table are thicknesses determined from magnified views of echocardiographic images.
The data shown considers only the 66 echocardiographic images for which both groups of investigators reported a pericardial thickness. The remaining 30 echocardiographic images were rejected by either the PSM investigators or the Mayo Clinical investigators, or by both. The reasons for rejecting images generally included absence of an EKG signal (needed to identify the appropriate part of the cardiac cycle to measure pericardial thickness) and poor image quality.
The difference in average pericardial thickness measured by the PSM investigators is statistically significant; the difference measured by the Mayo Clinic investigators is not.

Table 4-2
Differences Between the PSM Investigators' Readings and the Mayo Clinic Investigators' Readings (Paired Comparisons)

Parameter	Mayo Clinic Reading	PSM Reading	Percent Difference
Average pericardial thickness for the 66 echocardiographic images read by both teams of investigators	0.81 mm	1.09 mm	35 %
Average pericardial thickness for the 31 echocardiographic images from Vieques fishermen read by both teams of investigators	0.78 mm	1.16 mm	49 %
Average pericardial thickness for the 35 echocardiographic images from Ponce fishermen read by both teams of investigators	0.83 mm	1.04 mm	25 %

Notes: Data on Mayo Clinic readings and PSM readings presented by Dr. Ríos.
Percent differences are calculated as the difference between the two readings divided by the Mayo Clinic reading.
All differences between the Mayo Clinic readings and the PSM readings are statistically significant.

5.0 COMMENTS ON STATISTICAL ANALYSIS

This section reviews the panelists' comments on the statistical analyses of the Vieques Heart Study data. These comments were based largely on data that the PSM investigators presented at the meeting. Question Area 3 specifically asked the panelists the following: "How effectively does the statistical analysis minimize the possibility that chance, design, effects, or potential confounders account for the observed associations? Please consider the following:

- Appropriateness of tests, regression models, or other models used
- Methods to control for potential confounders
- P Value(s) and measures of association
- Impact of the issue of multiple comparisons"

Before the panelists addressed these issues, a PSM investigator presented data summarizing the information collected on potential confounders. For instance, he displayed the age distributions for the Vieques and Ponce populations, after which he showed data on marital status, alcohol use, and cigarette smoking. He then presented data on numerous self-reported co-morbid factors, including past diagnoses of high blood pressure, high cholesterol levels, diabetes, lupus, scleroderma, rheumatic fever, thyroid disease, tuberculosis, cancer, and heart disease. Of all the variables presented, only age had statistically significant differences between the study and control populations. Panelists noted that other variables had notable differences, even if these were not statistically significant. For example, 44% of the Vieques subjects reported having been diagnosed with high blood pressure, while 31% of the Ponce subjects reported the same outcome.

The panelists briefly discussed the information presented and whether additional statistical analyses should be conducted using the Vieques Heart Study data. Their comments addressed the following three general topics:

Recommended use of multivariate statistical analyses. Two panelists thought the PSM investigators should do further multivariate statistical analyses to rule out the possibilities that confounding factors explain the differences in pericardial thickness or that these factors mask even greater differences than originally reported. Both panelists explained that even variables without statistically significant differences between the study and control groups can be confounding factors, particularly for studies with relatively low sample sizes. They agreed that a multivariate statistical analysis considering a wider set of variables (not just age) is needed to eliminate potential confounding factors and to prove that the observed results are free of bias. One of the panelists referred to a journal article recommending a way to identify the variables to consider when testing for confounding factors: selecting all variables with statistically significant differences between study and control groups, with significance based on P values ranging from 0.2 to 0.5, rather than the much lower value (0.05) used by the PSM investigators.[17]

Other issues pertaining to statistical analysis. Throughout the meeting, panelists made several comments, suggestions, and recommendations about the statistical analyses of the Vieques Heart Study data. One panelist recommended that PSM investigators examine the pericardial thickness data more closely to determine whether the observed difference between the Vieques and Ponce subjects might result from one or two influential data points. Several panelists recommended analyzing how pericardial thickness varies with age and whether this variation differs between the two study groups. They suggested this analysis because age is probably the best surrogate for cumulative exposure to low-frequency noise in the Vieques population—therefore, age-dependent pericardial thickening might suggest a dose-response relationship. These panelists cautioned, however, that age should not be considered a direct marker of exposure to noise and further investigation would be needed to quantify dose-response, if such a relationship were found. The PSM investigators did not show any data on how the measured pericardial thicknesses varied with the subjects' age. Finally, in response to a participant's

concern that the Vieques Heart Study might have lacked statistical power to detect pericardial thickening, a panelist used the SPSS Sample Power module to determine that the study had 80% power of detecting an 0.15 mm difference in pericardial thickness with just 35 subjects in each group. He computed these figures using the standard deviations in pericardial thickness reported in the Vieques Heart Study. Considering this calculation, the panelist doubted the Vieques Heart Study suffered from a Type II error (i.e., failing to detect an outcome that actually exists).

Statistical analyses of measures other than pericardial thickness. When discussing recommendations for conducting additional statistical analyses, the panelists revisited an issue raised earlier in the meeting: evaluating the age-dependence of measurements other than pericardial thickening. To begin this discussion, a consultant to the PSM investigators reiterated that examining the age-dependence of these parameters could reveal notable trends not apparent from a simple comparison of the means of the parameters across the two study groups. For example, the data currently suggest that the average left ventricular mass of the Vieques population does not differ significantly from that of the Ponce population. But left ventricular mass is known to increase with age and the two populations differ in age, on average, by roughly 10 years. The panelists agreed that detailed investigative analyses of the available data might help generate hypotheses, but they reiterated their reservations about analyzing for outcomes (e.g., changes in functional and hemodynamic parameters with age) that were not part of the original study design (see Section 4.5).

The panelists expressed their specific concerns after viewing an example of the type of proposed age-dependent analyses. Specifically, a consultant to the PSM investigators displayed a scatter plot showing how deceleration time varied with age for the Vieques and Ponce subjects. A regression to the data points showed that the deceleration time increased with age for the Ponce subjects (as would be expected), but the deceleration

time varied little with age for the Vieques subjects. The consultant suggested that such notable differences in the age-dependence warrant further investigation.

Several panelists, however, were not convinced that the deceleration time data presented truly suggest a difference between the Vieques and Ponce populations and cautioned against over-interpreting these and other results. One panelist, for example, noted that the age ranges differ between the two populations, with the Ponce subjects being roughly between 20 and 75 years old and the Vieques subjects being between 30 and 70 years old. Examining the deceleration time data points between the two groups over a comparable age range (i.e., between 30 and 70 years old), this panelist noted that the trend between deceleration time and age appears to be similar between the groups. Another panelist agreed, adding that the youngest and oldest subjects from Ponce might be influential data points that drive the apparent difference in the correlations between age and deceleration time. Furthermore, noting that deceleration time varies with respiration, a participant indicated that a rigorous echocardiographic study of deceleration time would ensure that images were acquired in a systematic fashion, insofar as the subjects' respiration was concerned.

In addition to these concerns, four panelists cautioned that the small sample size might provide inadequate statistical power to detect age-dependent differences in any of the echocardiographic readings. First, after comparing the relationship between age and deceleration time for the Vieques Heart Study to a relationship he observed in a different study, one panelist suspected that the available data are of insufficient power to permit robust conclusions regarding pathologies among either the Vieques or Ponce subjects. Another panelist agreed and stressed that the PSM investigators would probably need to design a different study altogether to examine age-dependent cardiac function and structure. Such a study would require improved and systematic sampling from the age distribution, which was not done in the Vieques Heart Study. A third panelist added that

an improved study design would gather information on all potential confounders for all variables of interest (including deceleration time), rather than focusing on factors that can confound pericardial thickening. Finally, echoing the other comments, a fourth panelist recommended that the PSM investigators perform power calculations to determine the minimum sample size needed to detect an age-dependent result, before investing too much time examining these data.

In summary, the panelists recommended that the PSM investigators conduct multivariate statistical analyses to support their contention that confounding factors do not explain the observed difference in pericardial thickness. Most panelists supported the proposal to conduct more detailed analyses of the existing structural, functional, and hemodynamic parameters measured during the Vieques Heart Study. Because, however, the Vieques Heart Study was not originally designed to measure these parameters, the panelists cautioned that the number of subjects might not be sufficient to support robust conclusions.

6.0 COMMENTS ON INTERPRETATION AND INFERENCE

This section summarizes the panelists' responses to Question Area 4, "Interpretation and Inference." When responding to this question area, the panelists synthesized into summary statements the main findings on their overall impressions of the Vieques Heart Study. For reference, Question Area 4 included the following four questions:

"— Considering all of the foregoing, what is your interpretation of the meaning of the observed differences between exposed and control groups?

— What is the clinical significance of the findings?

— What is the public health significance of the findings?

— What further investigation, studies, or other actions are indicated (if any)?"

Discussions under this question area initially focused on specific topics, such as the role of "Core" Labs" in clinical studies. But then it addressed broader issues, such as the public health significance of the Vieques Heart Study and whether additional investigation of pericardial thickening is warranted. A summary of these comments, organized by topic, follows:

The role of the Core Lab in clinical studies and in the Vieques Heart Study. While discussing the differences in the pericardial thickness measurements between the PSM and Mayo Clinic investigators, several participants asked about the nature of the arrangement reached with the Core Lab (i.e., the Mayo Clinic). Specifically, a question was raised as to why the Core Lab readings would not be considered definitive, thus superceding the investigators' own measurements. But both an ATSDR scientist and a PSM investigator agreed, that no such understanding had existed. Rather, the understanding was that the Core Lab would conduct additional, independent readings of the PSM echocardiographic recordings.

The panelists then discussed the role of Core Labs in general, and how the involvement of a Core Lab in the Vieques Heart Study affects interpretation of results. First, a panelist explained that Core Labs are known for personnel with extensive experience in a given measurement. Researchers often send data to Core Labs to test the reproducibility of measurements using a given methodology. This panelist noted, and others agreed, that standard practice in clinical trials and other research projects is to accept as final all results generated by Core Labs. He added that, in his experience running a Core Lab, in only one instance had his laboratory's findings been rejected (a case in which the industrial sponsor of a study rejected findings unfavorable to its product).

Although the other panelists generally agreed with this characterization of Core Labs, they listed three reasons why the use of the Mayo Clinic as the Core Lab for the Vieques Heart Study was somewhat unusual. First, three participants noted that the Mayo Clinic does not routinely use transthoracic echocardiography to measure pericardial thickness and is therefore not extensively experienced with this measurement. Second, a participant indicated that Core Labs are typically asked to be involved with every aspect of data acquisition and interpretation to help ensure data quality. The Mayo Clinic, however, was not involved with acquiring the echocardiographic images for the Vieques Heart Study. Third, a panelist commented that standard practice is for Core Labs to generate all data for studies, yet both the PSM investigators and the Mayo Clinic researchers reported readings of the echocardiographic images from the Vieques Heart Study. For these reasons, several panelists and participants thought the Mayo Clinic’s role in the Vieques Heart Study was not that of a conventional Core Lab, but that of an independent, objective, and expert reader of the data.

*Similarities and differences between the PSM and Mayo Clinic readings*. When discussing the pericardial thickness data generated by PSM and the Mayo Clinic, the panelists highlighted key similarities and differences between the results. First, a panelist

argued that the group should not debate whether the PSM data are better than the Mayo Clinic data, or vice versa. Noting that both data sets were generated by competent laboratories, the panelist said the difference between the data sets most likely resulted from random measurement error in the readings. Another panelist agreed, explaining that the pericardial thickness data measured by PSM and the Mayo Clinic should have been reproducible if transthoracic echocardiography is indeed a reliable technique for detecting sub-millimeter differences in heart structures. The lack of reproducibility between the results, he argued, likely results from the fact that both teams were attempting to measure dimensions lower than commonly accepted echocardiography resolution.

Despite difficulty interpreting differences between the PSM and Mayo Clinic data, several panelists identified an important finding supported by both the PSM and Mayo Clinic readings: All subjects in the Vieques Heart Study, whether from Ponce or Vieques, had pericardial thicknesses less than 2.0 mm. Many panelists based their interpretations of clinical and public health significance on this observation.

Significance of the results. Despite the differences between the PSM and Mayo Clinic data and the limitations of echocardiography, several panelists thought the available data provide compelling evidence for the following conclusions:

- No gross differences in pericardial thickness occur between the Vieques fishermen and Ponce fishermen.

- The observed pericardial thicknesses for both study populations appear to be within the range found among healthy individuals.

- On neither structural nor functional parameters do any of the echocardiographic data suggest widespread cardiac pathologies in either study population.

One panelist thought these findings should be reassuring to the Vieques fishermen, given the potentially serious public health implications of the data reported in the earlier study.[3]

Inference. Two panelists and two participants commented on the inferences that can be drawn from the Vieques Heart Study. First, a PSM investigator emphasized that conclusions about noise-related health effects should not be drawn from the Vieques Heart Study, because the study was designed strictly to examine statistical differences in pericardial thicknesses; it was not designed to permit attribution of the differences, if any, to a particular cause. He observed that noise-related health effects might be present for other endpoints (e.g., hearing loss) that have not been studied. A panelist agreed, adding that establishing causal relationships can be quite difficult, especially considering the differences between the two study populations in the Vieques Heart Study (see Section 3). Noting that the Vieques Heart Study studied potential effects only among commercial fishermen, another panelist cautioned against inferring that the apparent absence of pericardial thickening applies to the Vieques population as a whole.

Suggestions for future work. Given that the Vieques Heart Study did not find gross differences in pericardial thicknesses between the Vieques and Ponce fishermen, several panelists recommended no further research into potential pericardial thickening on Vieques. One panelist commented specifically that additional research into this issue would likely find nothing more than subtle—and probably clinically meaningless—differences in pericardial thickness, which would accomplish little in addressing the overall health concerns of Vieques residents.

Two other Vieques Heart Study-related suggestions for future action were offered. First, a panelist recommended that the PSM and Mayo Clinic investigators prepare a joint publication comparing their data sets and commenting on the limitations of using

transthoracic echocardiography for measuring pericardial thickness. Second, a participant recommended that publications of the Vieques Heart Study highlight similarities between the two study populations (e.g., in terms of structural and functional heart parameters), rather than focusing on a single parameter exhibiting slight, if any, differences of no known clinical significance.

Following the discussion on interpretation and inference, one of the meeting co-chairs asked the panelists to prepare written summary statements describing their overall impressions of the Vieques Heart Study. (Some participants prepared summary statements as well.) The panelists were then given 2 hours to prepare these statements. (They were made aware that they would have a chance to edit their own comments prior to finalization of this report.)

Appendix E presents the panelists' summary statements. Some of the summary statements were edited for clarity and purposes of presentation. All expert panelists and participants who submitted summary statements, however, have reviewed the contents of Appendix E and indicated that the summary statements in this report accurately reflect their opinions regarding the Vieques Heart Study.

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Appendix A

List of Expert Panelists and Participants

Vieques Heart Study Review Meeting

Condado Plaza Hotel
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July 12–13, 2001

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Vieques Heart Study Review Meeting

Condado Plaza Hotel
San Juan, Puerto Rico
July 12–13, 2001

Co-chairs

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Appendix B

Biographies of Expert Panelists and Participants

Note: All expert panelists and participants reviewed and approved their respective biographies.

Vieques Heart Study Review Meeting
Biographies

HENRY BLACKBURN, M.D.

Dr. Blackburn is the Mayo Professor of Public Health at the University of Minnesota's School of Public Health in Minneapolis. He is also an emeritus professor of medicine at the same university's School of Medicine.

He received an M.D. from Tulane in 1948. After that, he interned at Wesley Memorial Hospital in Chicago and was a resident physician at the American Hospital in Paris, where he worked with cardiovascular surgeon Rene Leriche. He was medical officer in charge at the U.S. Public Health Service's operations in Salzburg and Munich. He was a fellow in medicine at the University of Minnesota in 1956. Later he became chief resident in medicine at St. Paul–Ramsey County Hospital. After this, he held a private practice in internal medicine. During the same period, he was a faculty member at University of Minnesota: he chaired the Laboratory of Physiological Hygiene from 1972 to 1983, was the head of the Division of Epidemiology from 1983 to 1990, and retired in 1996.

Dr. Blackburn's research fields are cardiovascular and chronic disease epidemiology, clinical trials, electrocardiography in population studies, and exercise electrocardiography and physiology. He served as project officer of the Seven Countries Study and was principal investigator for the Sudden Death Study, the Coronary Drug Project, the Minnesota Heart Survey, and the Minnesota Heart Health Program. He has served on the Advisory Council of the National Institutes of Health's National Heart, Lung, and Blood Institute; chaired the Medical Section of the American Association for the Advancement of Science; been a member of the National Research Council's Committee on Diet and Health; chaired the Councils on Epidemiology and Prevention (under the International Society of Cardiology and the American Heart Association); been a member of the Food Advisory Committee of the Food and Drug Administration; and served on the editorial boards of journals in cardiovascular and chronic diseases. He has also been a consultant to the World Health Organization and U.S./Russian and U.S./Japanese health treaties.

GARY H. CAMPBELL, PH.D.

Dr. Campbell is currently an environmental health scientist supervising a section in the Division of Health Assessment and Consultation at the Agency for Toxic Substances and Disease Registry. He has carried out and supervised numerous evaluations of environmental health involving federal facilities on the National Priorities List (also called Superfund).

He received a Ph.D. in microbiology and immunology from the University of Oklahoma Health Sciences Center in 1972. He has held research positions at the Walter Reed Army Institute of Research, the University of New Mexico Medical Center, and the Centers for Disease Control and Prevention. Dr. Campbell has published extensively in the peer-reviewed literature on the immunology of parasitic diseases, principally African trypanosomiasis and malaria. He has been a principal investigator for grants from the National Institutes of Health, the World Health Organization, and the Agency for International Development. His professional memberships include the American Society for Microbiology, the American Society of Tropical Medicine and Hygiene, and the American Association of Immunologists.

RICHARD B. DEVEREUX, M.D.

Dr. Devereux is director of the Echocardiography Laboratory of New York Hospital–Cornell Medical Center. He received a bachelor's degree from Yale University in 1967 and an M.D. from the University of Pennsylvania School of Medicine in 1971. Dr. Devereux has received certifications from the American Board of Internal Medicine (for internal medicine in 1974 and cardiovascular diseases in 1977), and the American Board of Echocardiography (1999). He has been Professor of Medicine at Cornell University Medical College and an attending physician at New York Hospital since 1992. Dr. Devereux served as a consultant to Rockefeller University Hospital in 1988. He is a fellow of the American College of Cardiology. He served for 8 years on the Epidemiology and Disease Control-1 Study Section at NIH, including 2 years as Chair. Many of his more than 300 peer-reviewed research publications deal with aspects of echocardiographic methodology or epidemiologic studies of various cardiovascular diseases.

W. DANA FLANDERS, M.D., D.SC.

Dr. Flanders graduated from the University of Vermont in 1972 (B.S.), the University of Vermont College of Medicine in 1977 (M.D.), and Harvard University in 1982 (D.Sc., epidemiology). He is licensed to practice in Georgia and Alabama, and is board certified in preventive medicine. He has been a professor of epidemiology for the past 10 years at Emory University School of Public Health. He has contracts for consulting work with several prominent organizations, including the Centers for Disease Control and Prevention, the American Cancer Society, and the Georgia Medical Care Foundation. His areas of interest include methodology, genetic epidemiology, environmental epidemiology, infectious disease epidemiology, and cancer epidemiology.

DAVID W. FLEMING, M.D.

Dr. Fleming is Deputy Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) and Deputy Director for Science and Public Health at the Centers for Disease Control and Prevention (CDC). In this capacity he provides leadership and direction in shaping policy and developing and using CDC's and ATSDR's capabilities in science and public health practice. He is the principal source of expertise and advice to the Director on science and public health programs. He oversees the CDC offices of Minority Health, Global Health, Women's Health, and the Associate Director for Science.

Dr. Fleming received his B.S. in biology from the State University of New York at Albany in 1975 and his M.D. from the State University of New York Upstate Medical Center, Syracuse, New York, in 1979. In 1984, he began his career as a CDC epidemic intelligence service officer in the Center for Infectious Diseases. From 1984 to 1986, he was a preventive medicine resident in the Office of Epidemiology, New Mexico Department of Health and Environment.

MIGUEL ÁNGEL GARCÍA FERNÁNDEZ, M.D.

Dr. García Fernández graduated from Central University of Madrid with first-class honors. He received his doctoral thesis summa cum laude, then served as a fellow in cardiology at Victoria Eugenia Hospital. He began his investigative career at Spain's National School of Thoracic Diseases as an associate with the Echocardiographic Laboratory. In 1990, he became Director of Non-Invasive Cardiovascular Imaging and chief of the EchoLab (one of the largest in Europe) at the Hospital General Universitario Gregorio Marañón. One year later he became an associate professor of cardiology. His investigations have been wide ranging but have focused on echocardiography.

Dr. García Fernández has written 12 books published since 1982. These include *Doppler Cardiaco* (Madrid, 1988), *Ecocardiografía Transesofágica* (Madrid, 1988), *Doppler Color en Cardiología* (Madrid, 1991), *Principios y Práctica del Doppler Cardiaco* (Madrid, 1995), *Doppler Tissue Imaging* (English, McGraw-Hill, Madrid, 1998), and *Práctica de la Ecocardiografía de Contraste* (Madrid, 1999).

MAURICIO HERNÁNDEZ-AVILA, M.D., PH.D.

Dr. Hernández-Avila has been director of the Center for Population Health Research, National Institute of Public Health, Ministry of Health, Mexico, since 1997. Concurrently, from 1997 to 1999, he was a visiting associate professor at Emory University's Rollins School of Public Health.

From 1988 to 1990, he was Director of Chronic Disease Surveillance and Director of Epidemiology at Mexico's Ministry of Health, as well as being a research associate in

the Department of Epidemiology at Harvard University's School of Public Health in the United States. Dr. Hernández-Avila received an M.D. in medicine (1980) and a diploma in statistics (1983) from the National University of Mexico's Medical School, then an M.S. (1984) and Ph.D. (1988) in epidemiology from Harvard University's School of Public Health.

Dr. Hernández-Avila is a member of the National System of Researchers, National Level III (since 1990), the National Academy of Medicine (since 1993), and the Academia Nacional de Ciencias (since 2000). He has participated in the General Health Council of the Ministry of Health, Medical School, Environmental Program (Environment and Health) (1995), and the Technical Consulting Council of ECO-PAHO. In 1996, he received the Premio Miguel Aleman Valdes de Salud. In 1995, he acted as president of the Epidemiology Committee of the Mexican Ministry of Health's National Council for Prevention and Control of AIDS. Dr. Hernández-Avila has published numerous papers pertaining to medicine and public health in Mexico and Brazil.

EDGARDO HERNÁNDEZ-LÓPEZ, M.D.

Dr. Hernández-López is the chief of the Cardiology Section at the V.A. hospital in San Juan and an Associate Professor of Medicine at the University of Puerto Rico's School of Medicine. He has also served as a consultant in cardiology at the San Pablo Hospital, Hospital Auxilio Mutuo, and Pavia Hospital. Dr. Hernández-López graduated from the pre-med program at the University of Puerto Rico in 1964 and received his M.D. from the University of Grenada in Spain in 1971. He was an intern and resident at the V.A. hospital in San Juan and received a fellowship from Baylor College of Medicine in Houston, Texas. Twice he received the Purdue-Frederick Award from the Puerto Rican Medical Association and is a Fellow of the American Heart Association Council on Clinical Cardiology. He has been a member and Fellow of the American College of Cardiology for over 25 years. Dr. Hernández-López has been involved in 15 research projects, participated in 15 meetings, authored or co-authored 23 publications, and written 65 abstracts.

EDWIN M. KILBOURNE, M.D.

Dr. Kilbourne graduated with honors from the Cornell University College of Arts and Sciences in 1974 and from Cornell University Medical College in 1978. He trained in internal medicine at the University of Alabama in Birmingham and in epidemiology at the Centers for Disease Control and Prevention (CDC). Dr. Kilbourne is a Fellow of the American College of Physicians and the American College of Preventive Medicine and is also board-certified in medical toxicology. After completing his postgraduate training in 1983, Dr. Kilbourne accepted a staff position in environmental epidemiology at what is now the National Center for Environmental Health, CDC. He spent 2 ½ years in Spain on a long-term special assignment during which he participated in the epidemiologic work-up of the toxic oil syndrome disaster. He became chief of CDC's (environmental)

Health Studies Branch on his return from Spain, and led CDC's epidemiologic work-up and response to the eosinophilia-myalgia syndrome in 1989. Dr. Kilbourne's other accomplishments include a key role in developing the electronic version of CDC's *Morbidity and Mortality Weekly Report.* Dr. Kilbourne's work in environmental epidemiology won CDC's coveted Langmuir Prize for excellence in epidemiology. He is the author of some 100 scientific publications. Returning part-time to clinical practice in the mid-1990s, Dr. Kilbourne sits as a member of the certifying subspecialty Board in Medical Toxicology. In December 2000, Dr. Kilbourne assumed his current position: Associate Administrator for Toxic Substances and Public Health, Agency for Toxic Substances and Disease Registry (ATSDR). In this position he continues his research and plays an influential role in the evolution and development of new programs in toxicology and environmental health at ATSDR and CDC.

MANUEL MARTÍNEZ-MALDONADO, M.D.

Dr. Martínez-Maldonado is the President and Dean of the Ponce School of Medicine. Previously, he was the Vice-President for Research at Oregon Health Sciences University and Associate Dean for Research at OHSU School of Medicine. For over 25 years he was a professor of medicine at Emory University in Decatur, Georgia (where he was also Vice Chairman of Medicine), the University of Puerto Rico, Baylor Medical College and Southwestern. He received his B.S. from the University of Puerto Rico in 1957 and his M.D. from Temple Medical School in 1961. He was a post-doctoral fellow at the University of Texas Southwestern Medical School at Dallas, in the Department of internal medicine. He was Chief of the Department of Medicine at the San Juan VA Medical Center for 18 years. Dr. Martínez-Maldonado is a member of the American Society for Clinical Investigation and the Association of American Physicians. He is a Fellow of the American Association for the Advancement of Science. He is a member of the National Academy of Science's Institute of Medicine and is the author of over 250 publications.

GEORGE A. MENSAH, M.D.

Dr. Mensah graduated (with honors) in biology from Harvard College and has a doctorate in medicine from Washington University. His postgraduate training, in internal medicine and cardiology, was at the Cornell Medical Center in New York. He has served on the cardiology faculties at Vanderbilt University and the Medical College of Georgia. He is board certified in internal medicine and cardiovascular diseases and holds fellowships in the American College of Physicians, the American College of Cardiology, the European Society of Cardiology, and the Council of Clinical Cardiology of the American Heart Association. Before joining the Centers for Disease Control and Prevention (CDC) in July 2000, he was a tenured professor at the Medical College of Georgia and Chief of Cardiology at the V.A. Medical Center in Augusta, Georgia.

His recent honors include the 1995 Searle Distinguished Research Award of the

International Society on Hypertension in Blacks, the 1997 Dr. Walter M. Booker Innovation Award, and the Year 2000 Hero Award of the Association of Black Cardiologists. He is a member of the American Heart Association's National Research Program Evaluation Committee and serves as the Vice-Chair of the Laennec Society Executive Committee of the American Heart Association.

Dr. Mensah is the chief of CDC's Cardiovascular Health Branch. He has overall responsibility for determining operational policy of the Branch and directing Branch activities to integrate and support CDC objectives for a national program for the prevention and control of heart disease and stroke.

ELIZABETH OFILI, M.D.

Dr. Ofili is a professor of medicine and Chief of Cardiology at Morehouse School of Medicine. She is also the director and principal investigator of the National Institutes of Health Center of Clinical Research Excellence (also at Morehouse). Dr. Ofili completed medical school at Ahmadu Bello University in Nigeria and received an M.P.H. at Johns Hopkins University in Baltimore, Maryland. She is a recognized expert on echocardiography. Dr. Ofili has an active interest in the mechanism of myocardial dysfunction, with particular emphasis on the role of ultrasound imaging modalities.

In collaboration with Dr. Morton Kern, Dr. Ofili developed and validated the method of analysis of the intracoronary Doppler spectral wave form that remains in use in patients with coronary artery disease and in physiologic studies of coronary flow reserve. As a recipient of the Preventive Cardiology Academic Award, Dr. Ofili established large clinical patient databases at Grady Memorial Hospital on congestive heart failure, chest pain, and hyperlipidemia. She received the Young Investigator Research Award earlier in her career for work on the physiologic basis of pharmacologic stress agents (dobutamine, adenosine, and dipyridamole) in a canine model of coronary artery disease.

Dr. Ofili is the president of the National Association of Black Cardiologists and an active member of the International Society on Hypertension in Blacks. Dr. Ofili serves on several national committees, including the Executive Committee of the American Heart Association's Council on Epidemiology and Prevention and the Coordinating Committee of the National Cholesterol Education Program. She is a member of the American Heart Association's Scientific Councils on Clinical Cardiology, Epidemiology and Prevention, and High Blood Pressure Research. She also served on the National Academy of Sciences' International Panel on Global Research and Development in Cardiovascular Diseases in Developing Countries. Dr. Ofili has published over 80 scientific papers, book chapters, and abstracts, and made over 150 scientific presentations on hypertension, dyslipidemia, heart failure, and coronary artery disease. She is a Fellow of the American College of Cardiology.

JAE K. OH, M.D.

Dr. Oh is a professor of medicine and consultant in cardiovascular diseases and internal medicine at the Mayo Clinic, Rochester, Minnesota. He completed his undergraduate course of study at the University of Pennsylvania in 1975 with honor, majoring in biochemistry. Dr. Oh graduated from Pennsylvania State University Medical School in 1979 and completed a residency in Internal Medicine at the Mayo Graduate School of Medicine in 1982 and a fellowship in cardiovascular diseases at the same institution in 1985. His main academic and clinical interests are clinical applications of echocardiography, pericardial diseases, diastolic function, and the use of echocardiography in clinical research. His NIH grant was just awarded to be the Echo Core Lab for the upcoming STICH Trial which will address the optimal treatment strategy in patients with ischemic heart failure. He has written and supervised more than 100 scientific publications. Dr. Oh authored *The Echo Manual*, now in its 2nd edition, a standard text in echocardiography.

JULIO PÉREZ, M.D.

Dr. Pérez is a professor of medicine in the Cardiovascular Division at Washington University School of Medicine and is the Director of Echocardiography at Barnes-Jewish Hospital in St. Louis, Missouri. He is attending the meeting as a consultant to the Ponce School of Medicine. He obtained his B.S. and M.D. degrees from the University of Puerto Rico, was trained in Internal Medicine and Cardiology at the V.A. hospital in San Juan, and finished his cardiovascular and research training at Washington University in St. Louis. Dr. Pérez is board certified in internal medicine and cardiovascular diseases, as well as in echocardiography. He is a Fellow of the American College of Physicians, the American College of Cardiology, and the American Heart Association, Council in Clinical Cardiology. He has written 175 peer-reviewed scientific publications, as well as two books on cardiac imaging using ultrasound.

MANUEL POSADA DE LA PAZ, M.D.

Dr. Posada de la Paz is director of the Toxic Oil Syndrome Research Center of the National Institute of Health Carlos III (Madrid). He also directs the World Health Organization's (WHO's) Collaborating Center for Clinical Epidemiology of Environmental Diseases. He has been a reviewer for Spain's National Agency of Prospective Evaluation in the fields of epidemiology and public health since 1997, and is a former member of the Extended Scientific Council of the Health Research Fund (FIS). Dr. Posada de la Paz was president of FIS's Technical Commission Number XVI, "Toxic Oil Syndrome (TOS) and Related Matters," from 1994 to 1997; he has also served as temporary advisor for various steering, scientific, and joint committees for the study of TOS under the WHO.

Dr. Posada de la Paz is a graduate in medicine and surgery of the Universidad

Autónoma de Madrid (1977) and received a degree with first class honors from the same institution in 1981, along with a Specialist in Internal Medicine designation (1982). He holds a diploma in methodology in research from the Health National School, National Institute of Health Carlos III (Madrid; 1992), and was designated a University Expert in Probability and Medical Statistics (1999) and Multivariate Analysis (2000), with first class honors, from the Universidad de Educación a Distancia.

Dr. Posada de la Paz edited the book “Toxic Oil Syndrome’s References” (1990) and belongs to the Spanish Society of Epidemiology, the International Society of Epidemiology, and the Spanish Society of Internal Medicine.

CARLOS RÍOS-BEDOYA, SC.D.

Dr. Ríos-Bedoya is assistant professor in the Departments of OB/GYN and Family Medicine at the Ponce School of Medicine. He also lectures at the Hospital La Concepción on epidemiology and biostatistics. Previously, he worked as an epidemiologist and biostatistical consultant for the Ponce Department of Health. Dr. Ríos-Bedoya received his M.P.H. with a focus in epidemiology from the University of Puerto Rico in 1987 and his Sc.D. from Johns Hopkins University, School of Hygiene and Public Health, in 1999. While at the University of Puerto Rico, he received a merit certificate for being an outstanding student. Dr. Ríos-Bedoya is a Fellow of the Institute for Health Services Research of the American Association of Medical Colleges. He has presented and published on topics such as HIV genotyping and depressive symptoms among Puerto Ricans.

JOHN RULLÁN, M.D., M.P.H.

Dr. Rullán is the Secretary of Health of Puerto Rico. He received a B.A. from Northwestern University in 1977, an M.D. from University of Puerto Rico in 1982, and an M.P.H. from Johns Hopkins University in 1984. Dr. Rullán performed his internship in medicine at the University Hospital in San Juan and his residency in preventive medicine at Johns Hopkins. He is board certified in preventive medicine. He was Puerto Rico's State Epidemiologist from 1987 to 1994 and served as the director for the AIDS Central Office at the Puerto Rico Health Department from 1990 to1994. Dr. Rullán served as the Centers for Disease Control and Prevention consultant to Spain from 1994 to 1996 and played a central role in starting the Spanish National Field Epidemiological Training Program. Later, he was Deputy Director of the Office of Epidemiology at the Virginia Department of Health. He worked as a consultant to the President/CEO of Triple-S Management Corp. before assuming his current position in 2001.

ROBERTO TORRES-AGUIAR, M.D.

Dr. Torres-Aguiar is the Director of Cardiovascular Services at St. Thomas Hospital,

U.S. Virgin Islands. He obtained his M.D. from the Universidad Autónoma de Barcelona in Spain in 1979, and trained in internal medicine at Norwalk Hospital (affiliated with Yale University) in 1982. He has a fellowship in cardiology from the Heart Institute of Texas (St. Luke's Hospital, Baylor College of Medicine). He is also a Fellow of the American College of Cardiology and the American Medical Association. Dr. Torres-Aguiar is board certified in internal medicine and cardiovascular diseases. He was the director of the Cardiology Intervention Division at the former Hospital Universitario José N. Gándara in Ponce, Puerto Rico.

JESUS VARGAS-BARRÓN, M.D.

Dr. Vargas-Barrón received his M.D. from Universidad Nacional Autónoma de México (UNAM) in 1971, and continued at UNAM in internal medicine until 1974. Dr. Vargas-Barrón studied cardiology at the Instituto Nacional de Cardiología Ignacio Chavez and echocardiography at the Hospital "Ramón y Cajal" in Madrid, Spain. Starting in 1982, he was a research associate in echocardiography at the Arizona Health Sciences Center at the University of Arizona. Dr. Vargas-Barrón is the head of the Echocardiography Department and Professor of Postgraduate cardiology at UNAM.

ROBERT C. WILLIAMS, P.E.

Assistant Surgeon General Robert C. Williams directs the Division of Health Assessment and Consultation (DHAC) of the Agency for Toxic Substances and Disease Registry (ATSDR). He has been assigned to ATSDR since 1985. Earlier, he served as chief of ATSDR's Health Sciences Branch and as an environmental engineering consultant. Earlier, he was assigned to the Center for Environmental Health, Centers for Disease Control and Prevention.

He received a B.S. in civil engineering and a master's degree in environmental engineering from Texas A&M University. Assistant Surgeon General Williams is a Registered Professional Engineer, is a Diplomate of the American Academy of Environmental Engineers, and serves, or has served, as an officer and member of national committees for several professional organizations, including the American Water Works Association, the Water Environment Federation, and the American Society of Civil Engineers.

As director of DHAC, Assistant Surgeon General Williams ensures that (1) public health assessments are prepared for all National Priorities List sites throughout the nation; and (2) assessment, consultation, and related health activities are implemented for communities near hazardous waste sites as necessary to protect the public health. DHAC plays a key role in the ATSDR mission of preventing or mitigating adverse human health effects as a consequence of exposure to hazardous substances in the environment.

PERRI ZEITZ, M.P.H.

Ms. Zeitz received a B.S. in environmental public health from West Chester University in 1995 and began work as an environmental health specialist for the Montgomery County Health Department, Division of Environmental Field Services. In 1998, she received an M.P.H. in epidemiology from Emory University's Rollins School of Public Health. Before joining the Agency for Toxic Substances and Disease Registry in 1999, she was an Association of Schools of Public Health Fellow in the Centers for Disease Control and Prevention's (CDC's) National Center for Environmental Health, Division of Birth Defects and Developmental Disabilities. While at CDC, she was part of a team that evaluated the effects of disinfection byproducts on adverse reproductive outcomes such as birth defects. Her current projects include serving as the principal investigator for a study to assess the long-term health effects of methyl parathion exposure in children and providing epidemiologic and technical support to states participating in the Hazardous Substances Emergency Events Surveillance system and the Program To Build Capacity To Conduct Site-Specific Activities.

Appendix C

Charge to the Panelists

Vieques Heart Study Review Meeting
Charge to the Panelists

The Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), and the Ponce School of Medicine (PSM) are holding a meeting of internationally recognized experts in cardiology and epidemiology to review a study of possible cardiac abnormalities in Vieques fishermen. The dates for the meeting have been set as Thursday and Friday, July 12-13, 2001 in San Juan, Puerto Rico. The meeting is co-sponsored by ATSDR/CDC and PSM.

Background

The Island of Vieques lies east of the main island of Puerto Rico and has approximately 9,000 residents. For several decades, the U.S. Navy has used the far eastern end of the Island as a practice ground for training exercises. The training has involved the use of explosive ordnance (bombs, artillery shells, and other explosive devices) which causes noise and vibration that are evident to inhabitants of the Island when training exercises are taking place.

There has been concern regarding possible adverse impact of Navy exercises on the health of Vieques residents. This concern has been particularly great during the last two years. One of the issues raised has been whether noise and vibration could have had an adverse health impact. Dr. N. Castelo-Branco and others in Portugal described a syndrome of cardiologic, neurologic, and immunologic findings in aircraft workers that they labeled “vibroacoustic disease.” Cardiac abnormalities noted by Dr. Castelo-Branco and colleagues included pericardial thickening and valvular abnormalities that were noted by echocardiography.

Acting on the hypothesis that Vieques residents might have developed abnormalities similar to those observed by the Portuguese investigators, PSM investigators sampled randomly from fishermen’s trade association lists to recruit subjects in Vieques and a comparison group of fishermen in Ponce. Subjects were studied by echocardiography, with readings done by the PSM investigators. At the request of ATSDR, CDC, and PSM, Dr. J.K. Oh at Mayo Clinic performed an independent reading of the same data. The findings will be reported by the investigators at the review meeting. In addition, we anticipate that a draft report of the study will be sent to investigators approximately one week in advance of the review meeting.

Purpose of the Meeting

ATSDR/CDC

The White House charged the Department of Health and Human Services (HHS) with scientifically evaluating reports of cardiovascular abnormalities occurring among residents of Vieques and potentially related to Naval training. The Secretary of HHS delegated this task to ATSDR and CDC. The Governor of Puerto Rico has also asked ATSDR/CDC to participate in this assessment. (ATSDR had been evaluating possible toxic health hazards posed by Naval training since 1999, when a Vieques resident petitioned

ATSDR's involvement.)

In consulting with PSM investigators, ATSDR/CDC has determined that their work raises a number of important questions on the frontiers of work in echocardiography, cardiology, and environmental epidemiology. Accordingly, ATSDR/CDC desires the assistance of qualified scientists to help evaluate and interpret PSM's findings. ATSDR/CDC will report its opinion on the significance of PSM's findings to the Secretary of HHS; this opinion will be based in part on input from the expert reviewers.

PSM

PSM is fully aware of the innovative nature of its approach to the scientific problem at hand. PSM's sole desire is to conduct a scientific investigation of the very highest quality. Accordingly, PSM welcomes the opportunity for expert review of its work, conducted by highly qualified scientific experts. PSM hopes that expert input provided by the reviewers will be reflected in its final report of the study for journal publication.

Extraneous Issues

Strong feelings exist as to whether the Navy should continue its training exercises on Vieques. Such sentiments are reflected in many recent media reports, legal action, and the statements of politicians in both Puerto Rico and the United States. Although these desires and views may be firmly held, they are extraneous to the purpose of the review meeting, which is scientific in nature. Accordingly, both ATSDR/CDC and PSM ask that reviewers evaluate PSM's study on purely scientific grounds, applying generally accepted scientific principles and standards of scientific practice.

Questions for Reviewers

Although any comments are welcome ATSDR/CDC and PSM ask that reviewers consider at least the following four areas (to the extent that each reviewer's experience and expertise permit):

1. Study design and data ascertainment
2. Echocardiographic measurements
3. Statistical analysis
4. Interpretation and inference

Definitions of Terms and Introduction to the Questions

For purposes of this document, the terms "epidemiology" and "epidemiologic" refer to observational studies. "Observational studies" are those that involve compiling data related to occurrences that are beyond the investigator's control. They are distinguished from experimental studies, and more specifically from randomized controlled trials (RCT's), by the absence of control over assignment to specific exposures or to treatment groups. (We understand that some would disagree with this definition and would characterize controlled trials as epidemiologic. We adopt the foregoing definition only for the sake of clarity.)

In its simplest form, an epidemiologic study examines the association of an exposure with a health outcome. In the Vieques Heart Study, the exposure is being a fishermen on Vieques, and the health outcomes measured are a variety of parameters measured via echocardiography. If an association of the exposure and outcome is found, there are four possible explanations:

1. The exposure (being a fishermen on Vieques) is a "cause" of the outcome
2. The apparent association is the result of a chance occurrence
3. The apparent association is due to bias
4. The apparent association is due to confounding.

Clearly, by "cause" we do not mean that fishing in waters close to Vieques would in itself cause cardiac changes. Rather, we mean that a fishermen in Vieques could be subject to influences that a control fishermen would not be subject to and that these influences would be the true cause of the findings. In this case, being a Vieques fishermen would place one in a causal pathway.

Of the four possible interpretations of an association, a "causal" explanation is the most interesting finding. However, to reach the conclusion that an association reflects a causal pathway, the alternative explanations of the finding of an apparent association (chance, bias, and confounding) must be excluded. The mention of these three negative-sounding terms should not be construed as an *a priori* indication that associations described in the Vieques Heart Study findings must be due to chance, bias or confounding. Rather, these terms are introduced because a proper review of *any* epidemiologic study should consider these concepts and their possible relevance to the study under discussion.

Interpretation of study findings includes deliberation regarding whether they reflect a causal pathway or one of the other possibilities. Thorough deliberation requires considering the impact of study design, measurement techniques, statistical analysis, and a variety of other factors affecting interpretation. The questions are divided accordingly.

Question Area 1 – Study Design and Data Ascertainment

- How effectively does the study design minimize the possibility that bias or confounding explain any of the observed associations? Please consider the following issues in your answer:

  - **S** Identification and comparability of sampling frames
  - **S** Sampling (of exposed and control persons)
  - **S** Non-response and measures taken to deal with it
  - **S** Ascertainment of non-echocardiographic information related to exposed persons and controls
  - **S** Availability of data on potential confounders

Question Area 2 – Echocardiographic Measurements

- Please comment on the echocardiographic measurements made, addressing (if relevant) the following issues:

  - **S** Sensitivity, specificity, and reproducibility
  - **S** Mechanical (machine-based) and human variability
  - **S** Blinding
  - **S** Interobserver and intraobserver variability of measurements
  - **S** Clinical significance of abnormalities noted

Question Area 3 – Statistical Analysis

- How effectively does the statistical analysis minimize the possibility that chance, design effects, or potential confounders account for the observed associations? Please consider the following:

  - **S** Appropriateness of tests, regression models, or other models used
  - **S** Methods to control for potential confounders
  - **S** P Value(s) and measures of association
  - **S** Impact of the issue of multiple comparisons

Question Area 4 – Interpretation and Inference

- Considering all of the foregoing, what is your interpretation of the meaning of the observed differences between exposed and control groups?
- What is the clinical significance of the findings?
- What is the public health significance of the findings?
- What further investigation, studies, or other actions are indicated (if any)?

Appendix D

Meeting Agenda

Vieques Heart Study Review Meeting

Condado Plaza Hotel
San Juan, Puerto Rico
July 12–13, 2001

Agenda

THURSDAY, JULY 12, 2001

7:30AM Registration/Check-in

8:00AM **Introductory remarks** . . . . . *Dr. Martínez, Meeting Co-Chair*
President of Ponce School of Medicine

8:15AM **Purpose of meeting and review of the charge** . . . . . *Dr. Fleming, Meeting Co-Chair*
Deputy Administrator of ATSDR

8:30AM **Background information on Vieques** . . . . . *Dr. Rullán*
Secretario de Salud

9:00AM **Background information on echocardiographic measurements** . . . . . *Dr. Oh*
Mayo Clinic

9:30AM BREAK

10:00AM **Presentation of the Vieques Heart Study** . . . . . *Ponce School of Medicine Faculty*

11:30AM **Comments and discussion on presentations**

12:00PM LUNCH

1:30PM **Discuss question area 1—Study Design and Data Ascertainment**

3:00PM BREAK

3:30PM **Question area 2—Echocardiographic Measurements**

5:00PM ADJOURN

FRIDAY, JULY 13, 2001

8:00AM	**Discuss question area 2** (continued)—**Echocardiographic Measurements**
9:30AM	B R E A K
10:00AM	**Discuss question area 3—Statistical Analysis**
11:30AM	**Prepare individual written comments on the topics discussed**
12:30PM	L U N C H
1:30PM	**Discuss question area 4—Interpretation and Inference**
3:30PM	B R E A K
4:00PM	**Conclusions/Recommendations**
4:30PM	**Finish individual written comments on the topics discussed**
5:00PM	**Concluding remarks from Co-Chairs** . . . . . *Drs. Martínez and Fleming*
5:30PM	A D J O U R N

Appendix E

Summary Statements Submitted by the Expert Panelists

Note: This appendix includes summary statements provided by the eight expert panelists and by three participants. The summary statements presented in this appendix are based on those submitted at the end of the expert panel review meeting. Some summary statements were edited and revised for clarity and purposes of presentation.

To ensure that the summary statements in this appendix accurately reflect their opinions, each author reviewed (and revised, if necessary) a draft copy of his or her comments and has verified that the summary statement in this appendix reflects his or her overall findings from the Vieques Heart Study expert panel review meeting.

Appendix E.1
Summary Statements Submitted by Panelist #1

The objective of the study is to examine the cross-sectional association of being fishermen on Vieques versus Ponce, Puerto Rico, with cardiac findings by echocardiogram. A primary hypothesis is addressed to differences in pericardial thickness, based on literature reports about a syndrome called vibroacoustic disease.

The findings measured in Ponce reveal a very small (0.15 mm.), statistically significant greater thickness of the pericardium of Vieques men compared to those from Ponce. The differences were not confirmed in a blinded examination of the same records at the Mayo Clinic. Means and four standard deviations from the mean in both clinics are within presumed (MRI-determined) limits of “normal” for pericardial thickness. No gross abnormalities were found of the cardiac valves or linings in either site.

Study Design and Data Ascertainment:

Identification of the occupational group by records of licensure appeared to be appropriate and complete. There was a higher response rate in Vieques despite a financial inducement to recruitment in Ponce. No data were collected on non-respondents. Of the basic demographic, historical, and physical measures only mean age was not comparable; Vieques fishermen were significantly older (10 years). Potential sampling bias and confounding were generally dealt with appropriately in the design.

Echocardiographic Measurements:

Effective measures were taken to reduce measurement error and observer bias, within the limits inherent in the tool and procedure. Echo findings overall, as well as geographic differences, were not clinically significant and no clear anomalies were found in either site.

Statistical Analysis:

Tests of measurement differences and population comparisons made were appropriate. Detailed data on potential confounders revealed no significant site differences except for age. One multiple regression analysis including age, site, and pericardial thickness revealed no significant age effect on the association of pericardial

thickness with site. Some half-dozen echo parameters were measured, which has a minimal impact on chance effect in multiple comparisons, particularly with the clear a priori hypothesis made about pericardial thickening.

Interpretation and Inference:

The statistically significant small mean difference in one of several echo measurements (pericardial thickness) made between Vieques and Ponce fishermen, with similar small but opposite findings in the validating lab, is within the range of values found for normal individuals; it is furthermore associated with no cases of clinically abnormal variants. The findings therefore have no apparent public health significance. They are not a good test for, but do not support, the hypothesis that exposure to low-frequency sound causes detectable vibroacoustic damage to the pericardium.

Conclusions and Recommendations:

The small differences in pericardial thickness measured in Vieques fishermen compared to those in Ponce are within the range of expected values for normals. No values approached those indicating pericardial disease in either region. The differences between measurements made in the two testing laboratories indicate the limited resolution, precision, and repeatability of echocardiograms for determination of non-diseased pericardial thickness. Despite the limitations of the method, the findings suggest that there is no pericardial disease in these occupational groups. The findings do not support the hypothesis of an effect on the pericardium of fishermen having different exposures to low frequency noise.

These findings say nothing about other potential effects of the war games on the health and well-being of Vieques citizens. They provide evidence that the echocardiographic ascertainment of other cardiovascular conditions than pericardial disease will require thorough prior documentation of hypotheses to be tested, along with substantially greater sample sizes and careful standardization of procedure.

Further studies and on-going monitoring are needed of the morbidity, mortality, and risk profiles of Vieques citizens as current plans are implemented to reduce their noise exposure and to improve the economy, health care, and public health of the area. This effort is desirable in any case and independently of issues of noise exposure and other potential long-term influences of the war games on the people or the ecology of Vieques.

Appendix E.2
Summary Statements Submitted by Panelist #2

Study Design and Data Ascertainment:

Study Objective: "To determine the occurrence of an association between the place of residence and cardiovascular changes in fishermen." This appears to be appropriate because the Vieques fishermen, by their propensity for fishing at the edge of the "danger zone," have the greatest exposure to noise from bombing/shelling. However, it is important that any conclusions about differences between Ponce and Vieques not be extrapolated to the non-fishermen population of Vieques because the populated land area on the island would be two or more times farther from the source of noise and hence would have been likely (by the inverse square law) to have been exposed to 1/4 of the acoustic/vibratory force.

Identification and comparability of sampling frames: Parallel ascertainment from fishermen's registry appears appropriate; the stated (in data that were not distributed to the review group) similarity of socioeconomic status and risk factors is also a positive attribute. Participants in Ponce were paid $15, based on a decision made during the recruitment, with no incentive needed in Vieques, to diminish a non-response problem in Ponce. The fact that many of the Vieques fishermen were members of two large extended families raises a currently unanswerable question about possible genetic influences on any study results. The partially selective nature of non-participation of Vieques residents and the possibility that some of the participants might have been in the group reported by Torres and thereby have influenced sonography performance if it were stated by the participant that he had previously had a thickened pericardium noted.

Sampling of exposed and control persons: Similar participation rates were obtained, albeit with use of a financial incentive in some Ponce participants and none in Vieques.

Non-response and measures taken to deal with it: The non-response rates were reasonably low. However, in view of evidence that non-participation was at least partially selective, it would be useful to request IRB permission to administer a brief questionnaire about individual characteristics and reasons for non-response.

Ascertainment of non-echocardiographic information related to exposed persons and controls: Additional data that were presented are given and discussed below.

Availability of data on potential confounders: Data on self-reported prevalences of a variety of potential confounders were presented. Measurements of height, weight and blood pressure were collected but not presented.

Echocardiographic Measurements:

Sensitivity, specificity and reproducibility: Extensive data presented by Dr. Oh documented moderate inter- and intra-observer reproducibility of echocardiographic pericardial thickness measurements with extensive efforts to standardize the methods of measurement. No generally accepted standard exists to define normal pericardial thickness, making it impossible to assess the sensitivity and specificity of findings for identification of pericardial thickening.

Measurements were made separately at the Ponce School of Medicine and at the Mayo Clinic, by different approaches. The concordance between measurements at Ponce and the Mayo Clinic was similar or slightly weaker than the inter- and intra-reader agreement at the Mayo Clinic. The data were derived by consensus in Ponce at a simultaneous reading session whereas at the Mayo Clinic measurements were made by sonographers with up to 20+ years' experience in quantitative research and all pericardial thicknesses were also measured by Dr. Oh, one of the world's leading authorities on pericardial disease. While the Ponce measurement approach has the appealing feature of involving a number of observers, the multi-faceted measurement protocol and the exceptional experience of the Mayo group with quantitative echocardiography for research purposes constitute even greater advantages. Therefore, the readings from the Mayo Clinic may be somewhat more reliable. At the meeting, it was suggested that both sets of data be included in the primary publication from this study, with emphasis that both sets of echocardiographic measurements yielded means that were well within what would be accepted as a clinically normal range, as were all individual data points.

Mechanical (machine-based) and human variability: Some sources of variability (machine used, sonographer, overall machine gain settings and frequency of the probe) appear to have been well standardized across the two study populations. The possibility that differential adjustment of the time-gain controls could have occurred cannot be assessed, because this was not systematically assessed at the time of recording. Potential effects of other factors such as depth of the focal zone also were not assessed.

Blinding: Readings were performed with appropriate blinding, including masking of dates, for both readings in Ponce and at Mayo.

Inter-observer and intra-observer variability of measurements: In paired analyses of studies with pericardial thickness measurements made both at the Ponce School of Medicine and the Mayo Clinic:

	Mayo	Ponce
Vieques (n=31)	0.78±0.15	1.16±0.20
Ponce (n=35)	0.83±0.15	1.04±0.24
	p=0.24	p=0.03

Ponce vs Mayo in entire population, $p<0.001$, with a significant difference in the conclusions of the study.

The most likely explanation for the overall difference is that the Mayo investigators adopted a comprehensive strategy to minimize confounding by additional echoes from off-axis structures, effects of high gain, etc., applying skill developed through years of extensive research experience in quantitative echocardiography. These refined technical approaches would be expected to result in lower mean pericardial thicknesses with less scatter of the data, yielding closer approximations of true anatomical thicknesses **if** the situation is similar to the extensive experience with left ventricular wall thickness measurements. Based on these considerations, the Mayo clinic measurements are likely to be more accurate (although not verifiable in the absence of data from a universally-accepted reference standard), leading to the conclusion that there is either no true difference or a minimal difference within the normal range in pericardial thickness between the fishermen from Vieques and Ponce. Dr. Oh also presented data on MRI measurements of pericardial thickness from papers in *Am J Radiol* 1985 (mean = 1.2 mm in diastole), *Am J Roentgenol* 1995 (1.7 mm, timing unclear), *Br J Radiol* 1998 (mean = 0.7 mm in thinnest area using high-resolution CT slices in 100).

Because measurements of trans-mitral blood flow velocities were made at the level of the mitral annulus rather than at the more usual level of the mitral leaflet tips, data are provided on the 95% confidence intervals for mitral annular flow measurements in normotensive, non-diabetic, non-obese black or white adults without significant valvular

heart disease in two large epidemiologic studies sponsored by the National Heart, Lung and Blood Institute are presented to help interpret the diastolic filling data:

	HyperGEN	Strong Heart Study
	(n=77, 55% male, 50±12 years)	(N=256, 54% male, 58±7 years)
'E' Velocity	43-102 cm/sec	35-92 cm/sec
'A' Velocity	41- 93 cm/sec	39-93 cm/sec
E/A ratio	0.59-1.65	0.49-1.57
Deceleration Time	120-288 msec	88-320 msec
Atrial Filling Fraction	0.21-0.46	0.21-0.53
IVRT	54-105 msec	NA

Clinical significance of abnormalities noted: By the Mayo clinic measurements, there is no difference in pericardial thickness between the populations, and therefore nothing to be of clinical significance. By the Ponce School of Medicine measurements, there is a small and statistically significant difference between the two populations. If one accepts the use of a crude and not well substantiated but nevertheless clinically reasonable partition value of 2.0 mm to identify pericardial thickening, not a single one of the participants in Vieques or Ponce had pericardial thickening by either the measurements made at the Ponce School of Medicine or at the Mayo Clinic.

Statistical Analysis:

Appropriateness of tests, regression models or other models used: Standard statistical tests were used in an appropriate manner.

Methods to control for potential confounders: Details concerning age effects were presented in the initial discussion but other potential confounders were not presented initially. Data on these potential confounders were presented on the second day.

Additional analyses suggested by Dr. Pérez led to a display of deceleration time versus age in the Vieques and Ponce populations, with somewhat higher values at younger ages in Vieques. All but 4 of the approximately 80 data points fell within the 95% confidence interval of the relation of mitral deceleration time versus age derived from 148 normotensive participants in another NHLBI-sponsored epidemiologic study.

P values and measures of association: Standard methods were used.

Impact of the issue of multiple comparisons: Because study power was calculated based on a hypothesized difference of 1 mm, the test of a difference between Vieques and Ponce fishermen was considered the primary hypothesis. Adjustment for multiple comparisons was not performed.

Interpretation and Inference:

Considering all of the information, what is your interpretation of the meaning of the observed differences between exposed and control groups? The conflicting findings of the presence or absence of a small difference in pericardial thickness well within the normal range for a difference between Vieques and Ponce fishermen do not provide convincing evidence of a true biological effect of the postulated exposure. The modest reliability of measurements between individuals, readings and centers suggests that small inter-group differences in the Ponce readings are more likely related to scatter of the data rather than to any real difference.

What is the clinical significance of the findings? Variation of pericardial thickness well within the normal range is of no known clinical significance.

What is the public health significance of the findings? If one accepts the use of a crude and not well substantiated but nevertheless clinically reasonable partition value of 2.0 mm to identify pericardial thickening, not a single one of the participants in Vieques or Ponce had pericardial thickening by either the measurements made at the Ponce School of Medicine or at the Mayo Clinic.

What further investigations, studies or other actions are indicated (if any)? With the evidence of either a zero or minuscule effect size of exposure to low-frequency sound on pericardial thickness, combined with the fact that this exposure is scheduled to come to an end in less than 18 months, there is not a convincing reason to study pericardial thickness further. The evidence derived from the analyses performed, despite some disagreement, provide clear reassurance that pericardial thickening is not present of a degree that would be significant in a clinical or a public health context. If there is interest in defining the potential impact of the documented high rates of various cardiovascular or non-cardiovascular diseases in Vieques residents or prognostically-validated measures of left ventricular mass, systolic function and diastolic filling, a larger echocardiographic survey of a more general sample of Vieques residents and a control group with more complete ascertainment of confounders could be of value.

Conclusions and Recommendations:

This study was designed to determine whether low-frequency sound may induce pericardial thickening or other cardiac abnormalities. The background literature suffers from numerous limitations that prevent it from establishing unequivocally the existence of "vibro-acoustic heart disease." The choice of Vieques fishermen as the primary case population is appropriate since they are likely to have been exposed to 3-4 times higher maximum sound intensities than other Vieques residents, but the latter fact precludes extrapolation of any results from this study to the 99% of Vieques residents who are not fishermen.

Good participation rates were obtained in both case and control samples, but with evidence of selective non-participation and an unknown possibility that some participation could have been influenced by participation in a previous uncontrolled study. Because of the small sample frames, the lack of information on characteristics of non-participants and reasons for non-participation is a limitation of the study, which may be correctable.

Measurements of pericardial thickness initially made by consensus of experienced clinical echocardiographers and a sonographer at the Ponce School of Medicine revealed a difference in pericardial thickness between Vieques and Ponce fishermen. Studies were then subjected to blinded readings by Dr. Jae Oh's highly experienced research team at the Mayo Clinic. Extensive data presented by Dr. Oh documented moderate inter- and intra-observer reproducibility of echocardiographic pericardial thickness measurements with extensive efforts to standardize the methods of measurement. The multi-faceted measurement protocol and the exceptional experience of the Mayo group with quantitative echocardiography for research purposes constitute advantages. Therefore, the readings from the Mayo Clinic are likely to be the more reliable ones that should be the primary basis for publications from this study. It is recommended that the Ponce and Mayo Clinic measurements be published jointly, to address as well as possible both the issue of appropriate methodology to assess pericardial thickness and the clinical significance of the results.

If one accepts the use of a crude and not well substantiated but nevertheless clinically reasonable partition value of 2.0 mm to identify pericardial thickening, not a single one of the participants in Vieques or Ponce had what would be considered clinically significant pericardial thickening by either the measurements made at the Ponce School of Medicine or at the Mayo Clinic.

Similarly, mean values and standard deviations of other measures of cardiac geometry and function were similar and normal in both groups of fishermen. Thus, no evidence of significant cardiac pathology associated with noise exposure in a small population of Vieques fishermen compared to fishermen from Ponce.

Appendix E.3
Summary Statements Submitted by Panelist #3

Study Design and Data Ascertainment:

The goal of the study was to determine if the pericardial thickness among fishermen who lived in Vieques differed from that among fishermen who lived in Ponce. The investigators selected study subjects from a sampling frame (registered Fishermen) in two areas, Vieques and a comparison area Ponce. Subjects were sampled randomly from the two areas. Participation was about 75 -80% in each area. They measured several potential confounders including self-reported hypertension, lupus, tuberculosis, scleroderma, and diabetes mellitus.

The study design was basically reasonable to accomplish this goal. However, two aspects of subject selection and comparability merit mention. The information on potential confounders was self-reported and medical care and completeness of diagnosis may have differed between the two areas. Thus one limitation reflects the likelihood that measurement of confounders may have been incomplete due to inaccuracies of self-reported information and differences in medical care. A second limitation which could have led to lack of comparability between the groups is that the two study groups were part of larger populations that differed in several ways including education, housing, medical care, frequency of selected diseases and so forth. Moreover, recruitment differed between the two groups, with one group receiving payment and the other not. More complete ascertainment and accurate ascertainment of confounders and use of identical recruitment methods should have reduced these potential biases. However, the extent, if any, to which these differences may have impacted estimated differences in pericardial thickness is difficult or impossible to know.

Echocardiographic Measurements:

Several issues, some of which are related, limit usefulness of the echocardiographic measurements of pericardial thickness.

The first limitation concerns the resolution of the machine. The resolution was about 1 mm, substantially less than the differences found between the groups being compared. In fact, the echocardiogram is not generally used for this purpose clinically.

The second limitation concerns the reliability of the readings. The investigators used a consensus method (blinded) to read and interpret echocardiograms. They also sent data to the Mayo clinic where a second blinded reading was done. The inter-rater and intra-rater reliability of these measurements were low (r^2 about 0.2), based on reading from the Mayo clinic. When the Mayo clinic readings were compared with those from

the Ponce School of Medicine (PSM), the r^2 was about 0.05, close to 0. This indicates that the degree of measurement error was large relative to the differences between the groups.

The third limitation concerns lack of established validity of the measurements. A gold standard was not available. However, if the measurements of pericardial thickness by PSM were correlated with the true pericardial thickness and if the measurements of pericardial thickness by the Mayo were also correlated with the true thickness, one would have expected the two measurements to be correlated with each other. The near zero correlation found suggests that the echocardiogram is not an appropriate way to measure small differences in pericardial thicknesses in these populations. However, one should also note that the echocardiogram should likely have been able to detect larger magnitude differences between the two populations (e.g, 3-4 mm).

A fourth limitation concerns the differential number of echocardiograms that could not be read 10 in Vieques, 1 in Ponce ViequesOR = 10, p = .04), usually because of no EKG. This suggests lack of standardization in application of the echo protocol.

A final limitation concerns the differential nature of the differences in the readings between the Mayo and PSM. The average reading by PSM was about .38 mm higher than readings by the Mayo for Vieques subjects, whereas the corresponding difference was about .21 for Ponce subjects. These differences appear to be statistically significant. Since both readings were done blindly, no explanation is obvious. However, the differences were very small, clinically unimportant and well within the limits of resolution and noise of the echo measurements. Nevertheless, use of the PSM measurements suggested that the pericardial thickness of the Vieques fishermen was higher on average than those of Ponce subjects where as the Mayo readings suggested the opposite.

Statistical Analysis:

The statistical analyses were basically sound, but further analyses would be helpful. We did not have a full array of descriptive statistics. Regression diagnostics, including identification of influential points and residual analyses would be useful. Further adjustments for covariates in the regression analyses were not done initially.

Interpretation and Inference:

The limitations inherent in use of the echocardiogram to measure pericardial thickness become dominant in a study such as this, if the differences between the populations are small. The study has documented effectively that the two populations have no large differences in pericardial thickness, but the measurement errors are large relative to differences between populations for populations with small differences. In this study,

the core lab (Mayo clinic) confirmed the basic echocardiographic findings (e.g., normal pericardial thickness estimates for each group), but did not confirm a statistical difference between the group.

In view of the low reliability, absence of validity assessment, poor correlation between PSM and Mayo pericardial thickness measurements, and the seemingly differential nature of the measurement error forces one to limit the conclusions that can be drawn from this study. In particular, the study suggests no *large* differences in pericardial thickness between the groups. However, limitations inherent in the echocardiogram for measuring pericardial thickness effectively preclude one from drawing conclusions about *small* differences.

In terms of causation, one must also limit interpretation strongly. The groups may have differed in many ways, both recognized and unrecognized. Even *if*, contrary to fact, large differences in pericardial thickness had been found between the groups, the cause of those differences would be unclear and might include many of the differences between the groups.

Background information about Vieques residents suggests that they have higher rates of several diseases, possibly including cancer, hypertension, teen pregnancy and cirrhosis. Priorities for future work in public health might better address these issues, rather than an obscure rather esoteric condition like pericardial thickening, a condition for which the scientific evidence linking it with noise is minimal at present and for which the clinical significance probably pales in relation to other public health and social issues.

Appendix E.4
Summary Statements Submitted by Panelist #4

Final Comments on the Vieques Heart Study:

- The data presented by Mayo Clinic Core Lab and the PSM investigators confirm that the pericardial thickness is within normal limits in the populations of both Vieques and Ponce.

- The data presented by the PSM group show a pericardial thickness in the Vieques group (1.20 mm) that is statistically different from the group of volunteers from Ponce Playa (1.04 mm). However, these results do not agree with those obtained from the Mayo Core Lab, which did not find significant differences in the thickness of the pericardium between the two populations studied.

- The differences between populations in pericardial thickness found by the Ponce group have no implications and can be explained in the light of the following commentary:

  1) The difference found (0.15mm) is below the current level of resolution of echocardiographic equipment.

  2) There are a great number of factors that can affect an echocardiogrphic measurement, and this is particularly true when one approaches the limits of resolution of the equipment. Many of these factors are difficult to control when one requires of the machine a millimeter level of precision. Among the most prominent of these factors are:

     - Gain of the machine: There was no standardization of the basic gain setting of the view from which the thickness of the pericardium was measured. (For example, measuring the pericardium at the minimum gain level at which the echos from the posterior wall of the myocardium disappear.) This factor was not controlled in the study and could have introduced a bias at the time of analyzing the results.

     - Axial and lateral resolution: The resolution of the equipment depends on the frequency of the transducer. The values of the thickness of the pericardium are probably beyond or at the limit of resolution of the machine. The image should have been acquired using the second harmonic, which substantially improves the

resolution of the machine.

- Other important factors that can affect the results are: the Pulse Repetition Frequency (PRF), logarithmic compression of the image, characteristics of the chest of the patient, and the quality of the study.

3) The problematic data found regarding interobserver variability and between-institution variability with the Core Lab indicate the lack of reproducibility of the measurement of pericardial thickness and the impossibility of its routine clinical use.

The conclusion is that the foregoing confirms the experience of echocardiographic laboratories around the world. Echocardiography lacks the sensitivity and specificity needed to definitively confirm or exclude small changes in pericardial thickness.

Accordingly, the small differences found have no clinical significance, as demonstrated by the fact that there was no difference noted in the evaluation of diastolic function. The differences probably represent a problem with the method.

Appendix E.5
Summary Statements Submitted by Panelist #5

The objective of the study presented and discussed over the review meeting was to verify previous reports regarding the high prevalence of vibroacoustic disease (VAD) previously reported among resident of Vieques. The prevailing hypothesis was that chronic exposure to intermittent episodes of noise, generated by military training activities that takes place in this island, was associated with a high prevalence of VAD.

To verify this hypothesis, researchers at Ponce School of Medicine studied fishermen with permanent residency in Vieques and compared them with fishermen who were residents of a comparable community in Ponce Playa. Exposure was defined as place of residency and the event of interest or measure of association was defined as the difference in pericardial thickness between groups, evaluated by echocardiography. Researchers estimated that they would need a sample size of 80 to be able to detect a 1 mm difference between groups, with errors type-I and II fixed at 0.05 and 20%, respectively.

Participants were selected from fishermen's license registration lists. In each place, a list of registered fishermen was obtained and from this list a random sample of individuals was selected and invited to participate in the study. A physical exam and general health questionnaire were applied to both groups to obtain information regarding potential confounders. Outcome measurements were obtained by echocardiography and read independently by two institutions: the Ponce school of Medicine, which used a consensus method, and The Mayo Clinic (the core laboratory), where two technician evaluated recordings and discrepancies between technicians were reviewed by a third experienced echocardiographer who made the final decision. Both institutions performed readings blinded to exposure status (i.e. place of residency). Both readings were used in the analyses.

The main hypothesis of the study was not rejected and it is safe to conclude that the mean difference in pericardial thickness between studied groups was not greater that 1 mm. However, it is important to mention that the size and direction of the estimated differences between Vieques and Ponce Playa, varied according to the institution that made the pericardial measurements. When researchers based their analyses using the Mayo Clinic's (the core lab's) outcome measurements, no statistically significant differences were observed; Vieques fishermen had lower pericardial thickness, and the estimated difference was 0.04 mm (0.78 vs. 0.82; $p>0.05$). In contrast, when the statistical analyses were based on the measurements provided by the Ponce School of Medicine, a small, but statistically significant difference (1.20 vs. 1.05; $p=0.003$) was

observed; fishermen from Vieques had higher pericardial thickness values, with an estimate mean difference of 0.154 mm.

Comments are based in the presentation of the study; no written report of results or study design was available for review. The study design has some problems that need to be considered in the final report:

1) The estimated sample size needed was not achieved. Researcher failed to account for non-participation rate in the study design. It is common practice to prevent this problem by expanding the estimated number of participants by a factor equal to the expected non-response of the study population.

2) Procedures used for participant recruitment were different between sites, a small economic compensation was offered in the control community, mainly to compensate for the larger non-response of this community.

3) Reasons or motives for non-participation were not investigated. Therefore we cannot ascertain or evaluate selection bias. It is highly speculative that people decided to participate or not in the study on the basis of factors related to pericardial thickness. Because of this, it is reasonable to assume that differential non-participation was not a serious problem.

4) No information was presented regarding other factors related or associated with exposure. Occupational histories were not reported. Similarly, no attempt was made to estimate cumulative exposure to noise in Vieques fishermen. We don't know if fishermen from Ponce Playa were exposed to other factors that could mask differences related to the exposure investigated (living in Vieques). However given that both populations had essentially normal values for pericardial thickness, this bias is unlikely to explain observed results. The questionnaire inquired about potential confounders and results based in multivariate analyses were essentially the same as those presented in the crude analyses, suggesting that with the limited samples size and confounders evaluated, confounding bias could not explain the observed results.

5) Healthy worker effect may be a source of bias if by selecting active fishermen; participants with VAD were preferentially excluded from Vieques. The observation that pericardial thickening is apparently not associated with any major or incapacitating disease suggests that this source of bias could not explain the observed results. However, the age difference between studied population (10 years younger in Vieques) may be indicative that in Vieques fishermen exit earlier from the working force, perhaps because of health effects. This difference may be indicative of some early health effect that may require additional analyses to be excluded as a source of selection bias.

6) The quality of echocardiography was different between groups, significantly more

echocardiograms were discharged or eliminated for the Vieques group. No information was reported regarding QA/QC followed during the study period. It is possible that the first group that was evaluated was Vieques and that this represents the normal learning curve. However it is not clear if this biased the results.

7) Although, both groups in a blinded fashion performed reading of echocardiography, the concordance rate between groups (Mayo vs. Ponce School of Medicine) varied across exposure groups. The concordance (measured by correlation) was significantly lower for Vieques. This last observation suggest the possibility for systematic bias. A more detailed analyses will be needed to assess the impact of this differential error as an explanation for the observed results. An additional explanation for the discrepancy observed between the Mayo Clinic and Ponce School of Medicine results is the large random error associated with measurement of pericardial thickness by echocardiography. Occurrence by chance is also a plausible explanation given that both groups were blinded to exposure status and the low correlation observed between measurements done by the two institutions (r=0.04), this low level of reproducibility suggest that random error is very large and thus may explain results.

8) Potential confounders were measured, but multivariate analyses were not presented in detail, given that weak associations are expected between outcome and potential confounders it is not likely that multivariate results may change the observed associations.

9) Statistical analyses need further development. The potential of using age as a surrogate of exposure should be explored, specially among the Vieques subgroup.

10) The public health significance of this data is limited by the sample size, the population that was studied, and the way in which exposure was ascertained. No extrapolation of these results should be made to other inhabitants of Vieques. I think that the only possible conclusion derived form the presented data is that there is no abnormal pericardial thickening in this sample of Fishermen from Vieques and Ponce Playa. Results support only the hypothesis that VAD, evaluated by echocardiography determined pericardial thickness, does not exist in either of the studied populations and thus it is not a health problem. It is important to underline that results cannot be extrapolated outside the studied population, thus results derived from the study do not reflect the health status of the population living in Vieques. Similarly, the observed study results do not in any way suggest that there are no health effects associated with war maneuvers or military activities that take place in Vieques.

11) Questionnaire data suggested potential differences between the studied populations, these differences should be explored with additional data analyses. Furthermore, a complete multivariate analyses of other echocardiography parameters is recommended. Multiple comparison could be an issue, however this may be accounted

by using a more conservative decision rule for significance.

12) In order to evaluate potential health effects of “war games” in the health status of population living in Vieques further studies are needed. Potential areas of evaluation could include: exposures to metals (aluminum, lead, uranium and other metals that may be found in bullets or explosives); stress generation by military practices and its impact in blood pressure, sleeping patterns, hearing, and other health events; economic and social impacts; other health effects related to noise and other health effects related to chronic exposure to stress.

Appendix E.6
Summary Statements Submitted by Panelist #6

Study Design and Data Ascertainment:

Cross sectional study of fishermen on Vieques island compared to fishermen on Ponce Playa in Puerto Rico. Study population came from a registry of fishermen in both places. Based on the sample size estimates, 80 cases will be needed to detect a 1 mm difference in pericardial thickness. (Note: Unclear if study design was for 80 cases plus 80 controls versus 40 cases and 40 controls; study group to clarify.) 80 random volunteers were identified from the Vieques registry. The control population of Ponce Playa had only 60 fiserhemen in the registry. In order to increase participation, $15.00 was offered and 42 eventually enrolled. Issues:

- Bias related to refusal to participate could not be evaluated because no further information was available for nonparticipants.
- Role of financial incentive unclear since money was offered to Ponce Playa, but not to Vieques fishermen.
- Ascertainment of nonechocardiographic information related to Vieques compared to Ponce Playa fishermen may be incomplete due to the nonequal access to health care and diagnostic services in Vieques and Ponce Playa.
- Availability of data on potential confounders; most of the data presented was based on recall of participants regarding potential confounders such as high blood pressure, diabetes, educational level, etc. Objective data such as blood pressure, weight, and blood sugar were not presented.

Echocardiographic Measurements:

The sensitivity, specificity, and reproducibility of echocardiography for measurement of the pericardium has not been established.

- Mechanical or machine based variability include the resolution of the technique (usually significantly greater than 1 mm) as well as the frequency of the transducer. Image quality is considerably affected by body size. Human variability is related to the image acquisition and adjustment of instrument settings.

It is possible to cause up to 3 or 4 mm difference in measurement of the same pericardium, based on the adjustment of the instrument "gain" as well as the "total gain control" or TGC. The TGC adjustment was not available to the reviewers.

Other human variability relate to the actual off-line measurements or analysis of the acquired data. Careful calibration as well as eye visualizing technique is required for reproducibility. For instance, on non-perpendicular or inferior/superior angulation of the echo reviewers' eyes relative to the structure of interest may change the measurement by 2 to 3 mm.

- Blinding could not be done for the technician acquiring the images due to the location of participants on different islands. The general awareness of the population or suspected health effects on Vieques may have contributed to a bias, but this could not be determined. It was suggested that reviewing tapes for length as well as TGC settings for both study populations may help clarify this.

- Interobserver and intraobserver variability of the measurements. This was available for the Mayo Clinic readings and was not significant. In 7 cases where there was mild (less than 0.2 mm?) variation, this was resolved by Dr. Oh, the core lab director. The measurements provided from Ponce Medical School were based on consensus review. It is not possible to evaluate interobserver or intraobserver variability in this case.

Clinical Significance of Abnormalities Noted: Overall the measurements for the cardiac structure and volume were similar for Ponce Medical School and Mayo Core Lab, and did not show any cardiac abnormalities on echocardiography or Doppler studies. Note is made that the measurements for the pericardium with magnification was as follows:

Population	Ponce Medical School	Mayo Core Lab
Vieques	1.20 +/- 0.23 mm	0.78 +/- 0.15 mm
Ponce Playa	1.05 +/- 0.24 mm	0.82 +/- 0.14 mm
P-level	0.003	NS

The statistical difference in Vieques versus Ponce Playa pericardial thickness measured by Ponce Medical School investigators is within the normal range of pericardial thickness by echocardiography (0.5 to 2.0 mm). The difference between institution measurements (i.e., Ponce Medical School versus Mayo Core Lab) is not significantly different, because it falls within the measurement error expected when a relatively thin structure is quantitatively evaluated by echocardiography.

Interpretation and Inference:

There is no significant observed differences in the pericardial thicknesses of Vieques versus Ponce Playa fishermen using echocardiography. The statistical difference that was observed only for the Ponce Medical School measurements cannot be interpreted, due to the level of noise of the measurement device and the intrinsic inability of transthoracic echocardiography to resolve a change of 0.15 mm as shown between both populations.

In any case, there does not appear to be any detected clinical significance based on the echocardiography measurements, since all were in the normal range for both Vieques and Ponce Playa fishermen, as measured by Ponce Medical School and the Mayo Core Lab.

Conclusions and Recommendations:

From the standpoint of any exposure to noise on Vieques contributing to cardiac abnormalities, this was not shown for the fishermen and sample studied. Based on the background literature that was provided, there have been no hemodynamic abnormalities, even when the pericardium was observed to be thickened. It is therefore not clear that further hemodynamic studies based on exposure to noise will yield significant differences. There may be a role for echocardiography in the evaluation of other structural and hemodynamic changes in Vieques inhabitants, based on general health risks. If undertaken, this study will need to control for other observed differences in high blood pressure and other covariates.

Appendix E.7
Summary Statements Submitted by Panelist #7

Background: Parts of Vieques island have been used for more than 60 years as a training area of the U.S. Navy. The intensity of the training activities is very high (more than 180 days per year). Many of the 9,000 Vieques residents are claiming different health problems theoretically related with the Navy's training activities. These claims are outside the scheduled discussion topics but the possibility of health effects caused by Navy training activities is contemplated in some fashion in the working hypothesis.

Working hypothesis or purpose: A general hypothesis is that the Vieques population is different from populations that live in Puerto Rico regarding cardiovascular pathology. The working hypothesis is that Vieques fishermen have cardiac abnormalities, when compared with fishermen of Ponce.

This kind of hypothesis is based on a theory of Portuguese scientists that exposure to certain types of sounds, which produce vibrations, can affect human health. The Portuguese team has named this hypothesis "Vibroacoustic Disease." There is no evidence in the scientific literature about this particular disease, based on searches done in Medline and Embase. There is only one monographic issue of the journal "Aviation, Space and Environmental Medicine" dedicated to this rare disease. This journal is not indexed in the most famous medical database.

Study design: The Vieques Heart Study was a cross-sectional study. The design of this study does not allow us to make inferences about causal relationships between the exposure (i.e., to noise) and the outcome (i.e., cardiac abnormalities). Since the exposure of concern has been occurring for decades, this reviewer questions: "Why didn't the study authors use a cohort study design to test this hypothesis?" Probably the authors had to conduct this study in a very short period of time due to both political and social reasons. Another possible explanation could be that they are initially looking for any evidence of association that might allow them to make further analytical investigations.

Sampling methods: Systematic sample in Vieques: 80 fishermen were sampled (beta error 0.2 and alfa error 0.05). Final N=69 were reachable. All of the fishermen from Ponce were selected. Final N=43. The sample size was calculated to identify 1 mm differences in the pericardial thickness measured by echocardiography.

Environmental factors: Registered fishermen at the time of the study were considered for the Vieques Heart Study. Sound was not measured.

Health outcomes: Cardiac abnormalities measured by echocardiography. Pericardial

thickness was the major target for this study although some other measurements were taken and compared between both populations.

Case definition: Registered fishermen on Vieques were considered. Exclusion criteria were not clearly specified. All subjects were males, and the race or ethnicity of the subjects was not predetermined. Members of the same family were not excluded and the possibility of some hidden genetic differences between Vieques residents and Ponce residents has not been able to be rejected.

Control definition: Registered fishermen in Ponce were considered. Exclusion criteria were not clearly specified. All subjects were males, and the race or ethnicity of the subjects was not predetermined.

Confounding variables: Some variables such as age, diabetes, high blood pressure, and autoimmune diseases were included, but not others like background on viral infectious that could have been addressed using proxy questions. The study should have included a number of counfounders relevant to pericardial diseases. However, controlling for confounding factors could only have been relevant in the case of the pericardium having really been affected.

Intervention: Both one- and two-dimensional echocardiograms were acquired for each of the participants. Several parameters were measured from the images that were acquired. A questionnaire was also used for the rest of variables. Most of these other variables were collected as an established diagnosis and were not based on direct measurements made by the investigators. The same technician did the echocardiographic examinations in both cities for all of the participants. She was not blinded at the time of the study. The calibration of the machine was the same in both cities. The authors used the same machine in both places. All echocardiographic images were stored as digital images, which were blinded for reading purposes. Observations:

- The pericardium size is more difficult to measure than are other cardiac structures; as a result, the variability in the pericardial thickness measurements is quite broad.

- The possibility of a systematic bias due to the fact that the technician was not blinded to the case and control groups cannot be rejected.

- Some settings on the echocardiogram machine *(e.g., gain)* were adjusted during the examinations, as is typically done. It is not possible to determine if the variable settings had any influence acting as a systematic bias (information bias).

Statistical analysis: The results were presented using a t-test (differences between means of the groups). The authors claimed that all variables had normal distributions. This is essential to apply this kind of test. A non-parametric test should have been used for comparing variables that are not normally distributed. Only univariate analysis were shown.

Other methodological issues: All images read by the Ponce School of Medicine were sent to Dr. Oh of the Mayo Clinic. He and other collaborators from the Mayo Clinic (ECHO Core Lab) measured the pericardial thicknesses, while blind to the location of residence of all subjects. They also analyzed the inter- and intra-observer variability of their measurements. The R^2 for inter- and intra-observer variability was very poor. At the same time, the comparison between the measurements done by both team of experts (Ponce and Mayo) for a single subgroup of participants (31 from Vieques and 35 from Ponce) and using the same methods was also quite poor (R^2=0.046)

These data clearly showed that the original results have been influenced by a misclassification bias. When this type of misclassification is differential (i.e., Vieques present measures higher than Ponce) the final results is biased towards significance. But when this type of bias is not differential the final results tend to the null hypothesis. In this occasion the results offered by the Dr. Oh suggest that the bias is random or not differential. This would tend to reduce the real level of statistical significance.

Results: According to the measurements made by the Ponce School of Medicine, the only result that shows any statistical significance ($p < 0.03$) was the comparison of pericardium thickness:

Vieques:	1.2 mm ± 0.23	N = 43	10 echo readings rejected
Ponce:	1.05 mm ± 0.24	N = 41	1 echo reading rejected

According to the measurements made by the Mayo Clinic:

Vieques:	0.78 mm ± 0.14	N = 34
Ponce:	0.82 mm ± 0.14	N = 35

The Mayo Clinic investigators reported that they could not read pericardial thickness in 29 of the total readings. The Mayo Clinic worked in blind conditions and the distributions of these 29 participants are not known to the author of this report.

Note: When doing paired comparisons (i.e., considering only those subjects with

successful readings by both teams of investigators), the results of the analysis were the same: Ponce School of Medicine found a statistically significant pericardial thickening and the Mayo Clinic did not.

Overall observations:

There are different methodological problems with this analysis. The response rate among the Vieques fishermen is very low and the small differences in pericardial thickness found in the PSM analysis could be explained by eliminating a small group of participants. Further, the negative results found in the Mayo Clinic are not valid for comparison purposes because they were obtained from a small fraction of the initial sampling frame. We do not know about the real causes for not participating. This would have been investigated if some relationship of interest existed.

However, the work done by the Mayo Clinic is very useful for other purposes. Because we do not have any "gold standard" for measuring pericardial thickness, this work showed that the real reliability of pericardium measurements by echocardiography is very problematic, at least when we are trying to identify differences in a range of 0.5–2.0 mm. This is the area where the noise of the echo machine is higher than the reported difference in pericardial thickness, and the variance of this measurement suggests that use of echocardiography to measure fine differences in pericardial thickness is not valid. This contribution has been very important. The Mayo Clinic results could explain a major random effect that the authors expected at the beginning of the study. This has been the first time that these difficulties have been demonstrated by two independent laboratory readings.

One question is still pending, if the differences between the Vieques and Ponce fishermen had been greater than 3 or 4 mm, would echocardiography have been capable of detecting these differences? In that case, the variance of the measurements probably would not have had the same effect.

Conclusions: The results of the cross-sectional study suggested the presence of a minimal difference (although with statistical significance) in pericardial thickness between the Vieques and Ponce fishermen, but they do not allow us to confirm that there is a real association between being a fishermen in Vieques and any pericardium thickening. The reported small difference could be due to any combination of these factors:

- *Selection bias*. Lower response rate and elimination of different participants in a nonrandom fashion

- *Information bias*. There are several possibilities here: the technician that did the echocardiography was not blinded; age differences between the groups; timing

of either exploration or reading were not recorded (the latter was made blinded); and calibration of equipment. I do not want to say that all of these possibilities would have acted or they have any relevance; but, in the presence of small differences, it is difficult to make any conclusion in regards to this health outcome, with the possibility of these biases.

- *Misclassification bias*. There was probably **non-differential** bias as both the cardiologist experts and the ECHO Core Lab report came to an agreement stating that the error on measuring pericardial thickening was a random error. If this was so, a random error would have produced the same effect in both groups of participants and thus the results would lead to the null hypothesis. However, the authors reached a significant result ($p<0.03$) and from my point of view this means that it is very difficult that the random error on measuring can justify by itself these results. In my opinion, only the presence of a **differential bias** – non random error – or a mixture of small different bias together with a very low quality of the outcome measured could explain these results.

- *Confounding*. Albeit I do not really think that potential counfounders not included in the study could have biased the results, the authors should have taken these into account to avoid the suspicion that they might have acted. To assume that some of the agents that potentially could have caused pericarditis could be confounding variables is almost equivalent to saying that the Vieques' residents have a silent pericardium pathology.

An impact on public health of activities occurring on Vieques can not be rejected based on the results of a study that has been performed under less than optimal circumstances (social pressure). In addition, other data seem to indicate that there might be major health problems in the Vieques population; these problems would not be identified in this study, which was limited to fishermen. The implication is that it is necessary to continue to study the health status of the Vieques population, including cardiovascular pathology in a well designed study without external pressures or limitations. In the meantime I would suggest applying the "precautionary principle" and stopping certain activities until all of these issues have been clarified.

Note: Some of the figures stated in this report were obtained from notes taken during oral presentations made by investigators from the Ponce School of Medicine. If we had a complete written report, our comments would have had others nuances; but no such report was available.

Appendix E.8
Summary Statements Submitted by Panelist #8

My comments are limited exclusively to the echocardiographic aspects of the study:

My impression is that the Portuguese investigators' publication and their echocardiographic findings in some way influenced the Vieques study. Nevertheless, we need to point out that although the echocardiography provided isolated reports detecting a thickened pericardium, other imaging methods, such as computerized tomography or magnetic resonance, are probably superior and more reliable for this diagnosis. Because of this, echocardiography is not used routinely for this purpose. However, and very likely due to the geographical situation and the difficulties in transporting other cardiological diagnostic equipment, they decided that the study of the Vieques population would be conducted using ultrasound.

The results obtained in Ponce and in Vieques, other than exhibiting a small difference from a statistical point of view, show no significant clinical difference. I am convinced that the work of both the physicians from the Ponce Medical School and the Mayo Clinic was done with strict scientific rigor. The small observed differences were related to the technical limitations of the echocardiographic equipment (image resolution).

Given the results obtained up to this time, it is not possible to conclude definitively as to the significance of the study as it relates to public health. It is necessary to continue with additional research studies.

Due to the difficulty of transporting CT or MRI equipment, one alternative is transesophageal echocardiography. With this technique, in addition to exploring more extensive areas of the pericardium, it is possible to obtain more precise information about the functional and anatomical state of the cardiac valves—especially of the mitral and aortic valve leaflets. In addition, the study of diastolic function could be complemented with an analysis of pulmonary venous flow.

Finally, I'd like to suggest that for future medical research studies of the Vieques population, other clinical areas—not only focused on cardiac function—should be investigated.

Appendix E.9
Summary Statements Submitted by Participant #1

The role of the Mayo Echo Core Lab for the Vieques Heart Study (or Ponce Echo Project) was to provide independent reading and measurements of echocardiographic parameters obtained by the Ponce Medical School for the Vieques Heart Study. Ninety-four studies in 7 CD's were mailed to the Core Lab from the Ponce Medical School investigators in digital format. This document includes the measurement procedure by the Mayo Echo Core Lab, measurement variables, and my personal interpretation and recommendation regarding the Vieques Heart Study.

Operating Procedure for Echo Core Reading

The aim of Vieques Heart Study was to compare the cardiac structure and function of fishermen living in Vieques with control subjects living in Ponce. The study was prompted by a preliminary finding that cardiac structure(especially the pericardium) is thicker in the individuals exposed to low frequency noise such as noise generated by US Navy bombing in Vieques.

Total number of affected and control subjects was 94 and their studies were sent to the Echo Core Lab in *avi* digitized format. Each study included standard transthoracic echocardiographic views by 2-D imaging and Doppler/color flow imaging. Once the studies arrived in the Echo Core Lab, the quality control, variability assessment, and analysis of all 94 studies were completed within 21 days. The reviewers were blinded to clinical data of the study subjects. The following are the parameters measured and/or calculated by the Core laboratory:

1. *M-Mode*
    a. Aortic root size (diastole)
    b. Left atrial size (end-systole)
    c. Aortic valve opening (mid-systole)
    d. LV septal thickness (end-diastole; standard way)
    e. LV septal thickness (end-systole)
    f. LV posterior wall (end-diastole; standard way)
    g. LV posterior wall (end-systole)
    h. LV internal dimension (end-diastole)
    i. LV internal dimension (end-systole)
    j. Mitral valve E-point-septal-separation
    k. LV fractional shortening (%)
    l. Mitral valve DE amplitude (early diastole)
    m. Pericardial thickness (end-diastole) from standard, non-magnified — Mode views at the level of the LV papillary muscles
    n. Pericardial thickness (end-diastole) from the 3.0 X magnified M-Mode views

where the pericardium is displayed alone **(see "note" below)**

o. LV mass (in gm; using the Penn convention; or alternative method in the Core lab)

2. *Two-dimensional echocardiogram*

a. LV outflow tract diameter (mid-systole, long-axis view)
b. LV volume (end-diastole, 4-chamber, Simpson's rule)
c. LV volume (end-systole, 4-chamber, Simpson's rule)
d. Ejection fraction (%)
e. LA volume (end-systole; 4-chamber)

3*. Doppler*

a. LV outflow tract time velocity integral (cm.;5-chamber)
b. R-R interval (sec.)
c. Heart rate (min-1)
d. Stroke volume (ml)
e. Cardiac output (L/min)
f. Mitral E (tips, cm/s)
g. Mitral A (tips, cm/s)
h. Mitral E/A ratio
i. Mitral deceleration time (ms)
j. Tricuspid regurgitant jet velocity (m/s)
k. Pulmonary vein pattern (S or D; presence of A reversal >20 cm/s)
l. Pulmonic valve flow time-to-peak flow (ms)
m. Descriptive (present or absent) and assessment (mild, moderate, severe) by color flow mapping of: 1-Mitral regurgitation; 2-Aortic regurgitation; 3-Tricuspid regurgitation; 4-Pulmonic regurgitation

Note: When measuring the pericardium in the magnified M-Mode views, the investigators at the study site employed the following approach (considering the fact that the dimensions of the electronic calipers in the Agilent system, where the images were acquired and initially measured, are small enough for this purpose): using a magnifying glass, the electronic caliper was moved until the crosshair section (dark) of the caliper was noted to initially touch the leading edge of the boundary; then it was set there and the second caliper was moved, again under a magnifying glass, until it touched the trailing edge of the pericardial boundary.

Summary of Data Acquisition and Image Reading:

Echocardiographic examination was performed by one sonographer using an Agilent cardiac ultrasound equipment with the fundamental imaging transducer (2 MHz). M-mode, 2-D, Doppler, and color flow imaging studies were recorded which were subsequently digitized in still frames and real-time images using “avi” files. The echocardiographic data stored in the CD’s were transferred to the Digisonic work station. For each view, a calibration was performed prior to any measurement. For measurement of small dimensions such as the thickness of the pericardium, a magnifying glass was used to guide the placement of caliper’s cross-hair at the leading and trailing edge of the pericardium.

Two primary reviewers who are experienced research sonographers performed the initial measurements required for the study. The third sonographer who is the coordinator of the Mayo Echo Core Lab repeated the same measurements in total of first 30 patients (15 from each of two sonographers’ pool). For the measurement of pericardial thickness, the third sonographer repeated in all patients. The Core Lab director also measured the pericardial thickness in all patients and reviewed all echocardiographic studies. When there was a considerable difference (>10%) between sonographers’ measurements, those measurements were repeated by the physician Core Lab director (in less than 1% of all variables). If echocardiographic images were difficult for measuring, those variables were not measured and documented as such. Two primary sonographers remeasured the same variables one more time 10 days or longer after the initial measurement in 20 patients (10 patients each) to obtain intraobserver variability in their measurements.

The measurements by the Core Lab were performed independently without the knowledge of study groups, clinical information, and each other’s measurement result. Prior to initiating the measurement of this study, M-mode echocardiograms of 20 subjects from recently completed NIH-funded study were measured for the same variables as the Ponce Study by two primary reviewers to standardize their measurement technique. The same set of data were measured by the Ponce investigators once as a group, but the individual data from the Ponce investigators were not shared with the Mayo Echo Core Lab.

Study Design and Data Ascertainment:

The primary hypothesis of the study was that pericardium is thicker in subjects living in Vieques than the individuals from Ponce, measured by echocardiography. At the same time, other cardiac structural, functional (systolic and diastolic), and hemodynamic differences between two groups were searched. The primary hypothesis was based on a previous finding that there was a significant difference in the pericardial thickness (4.0 vs 0.95 mm) measured by two dimensional echocardiography. The sample size was

calculated using a more conservative difference (the difference of 1 mm, rather than 3 mm) in the Vieques Heart Study. It appears that proper clinical and other potentially relevant non-echocardiographic data were gathered. In the end, however, the age of the Vieques subjects was about 10 years older. Although the difference may result in different values for some echo variables, it should not affect the pericardial thickness in normal individuals.

I am not aware of any published study which used echocardiography to measure the pericardial thickness as a study endpoint. To be certain about the significance of any difference in echocardiographic measurement of pericardial thickness, the difference should be greater than what the resolution of 2-D echocardiography allows. The primary hypothesis in this study was based on a previous observation which needs to be vigorously reviewed. We should also address the importance (or lack of importance) of increased pericardial thickness without clinical symptoms of pericardial diseases.

Echocardiographic Measurements:

- *Measurement of pericardial thickness by Echocardiography*. Echocardiography is the best available noninvasive imaging technique to evaluate cardiac structure, function, and hemodynamics at one setting with great portability. However, it has been well appreciated that there is substantial intra- and interobserver variability in echocardiographic measurements. The accuracy of echocardiographic measurements depends on multiple variables such as the quality of the examination, the type of measurement, frequency of transducer, the degree of resolution, the type of ultrasound equipment, measurement technique, measurement equipment, and the experience of involved personnel. The normal pericardium is a thin structure (less than 2 mm) around the heart. For this study, posterior pericardial thickness was measured from the M-mode echocardiogram from the parasternal view. It is well appreciated that echocardiographic measurement of the pericardium can be difficult since it is affected by gain setting and the resolution of transducer. A study from Pandian et al. documented the gain dependency and overestimation of pericardial thickness by echocardiography. There is no data I know to determine the degree of difference in the measurement of normal pericardium if the structure is imaged in two separate times.

  The pericardium is usually an innocent structure, but can be affected by multiple factors: infections, immunologic disorder, malignancy, radiation, trauma, endocrine disorder, etc. Therefore, it will be difficult to correlate the pericardial thickness with one definite etiology especially when there is no clinical manifestation of pericardial disease.

- *Evaluation of diastolic function*. Diastolic function is one of powerful predictors

for cardiovascular morbidity and mortality. Although there are multiple parameters, deceleration time (DT) of mitral inflow is most commonly used. It is affected by hemodynamically significant pericardial disease and is essential in the diagnosis of constrictive pericarditis which is usually caused by thickened pericardium. It is obtained by placing a sample volume in the mitral leaflet position during diastole. In the Vieques study, however, the sample volume was positioned in the mitral annulus. What complicates more is that there is respiratory variation in mitral inflow velocity and DT in patients with hemodynamically significant pericardial diseases. Therefore, diastolic function measurement in the Vieques study is difficult to interpret.

Another confounding factor for DT measurement is that there are numerous factors affecting DT such as age, hypertension, CAD, etc. Additional diastolic parameters can be of help such as pulmonary vein velocities, tissue Doppler imaging, and hepatic vein velocities. Those measurements were not obtained in the Vieques Heart Study.

- *Echocardiographic measurements by Ponce and the Mayo Echo Core Lab*. I was very impressed that there was such good concordance in the measurements of nearly all echocardiographic variables by two independent teams. The Ponce investigators with less experience with echocardiography should be congratulated for their excellent work. The only small difference was the pericardial thickness measurement. There was 0.15 mm difference (which was statistically significant) between two groups by Ponce investigators and no difference by the Mayo Echo Core Lab. The measurements, however, were within normal limits (1.2 mm or less). The possible explanations for the discrepancy are as follow:

  1) Echocardiography is not able to differentiate such a small difference in the thickness of cardiac structure.
  2) The difference in measurement equipments and techniques. The Ponce investigators used on-line Agilent unit and the Mayo investigators used Digisonic off-line measurement technique.
  3) The Ponce group measured as a group and the Mayo measured independently by three individuals.

  Probably, a combination of all three factors account for the small difference in the pericardial thickness. The more important and relevant issue is how we interpret the data which was the purpose of this meeting of internationally recognized experts in echocardiography, epidemiology, and public health. We should address the following:

  1) Is it important to the health care of the Vieques residents to demonstrate

the very small difference in measurement which is known to be difficult?

2) What is the clinical relevance?
3) Why was only the pericardium affected among many other cardiac structures?

There should be an explanation of the data presented at this meeting. I think it is most reasonable to publish the data from two independent readers and provide several possible explanations as above. It will be hard to convince the echocardiologists and cardiologists that 0.15 mm difference in pericardial thickness between two groups is a reproducible and clinically significant result.

For the primary hypothesis of the Vieques Heart Study to be tested, a gold reference technique for measuring the pericardium such as high resolution CT or MR should be used. However, even those imaging techniques won't produce data to suggest clinically significant health hazard related to the increased pericardial thickness since the pericardial measurements in subjects were within normal limits. There are numerous other social and health issues in the Vieques intrinsic to the region which can be better served by further studies other than measuring the pericardial thickness by any imaging technique.

Conclusions and Recommendations:

The Vieques Heart Study was a well planned prospective study to reevaluate a previous observation that cardiac structure is thicker in Vieques residents, possibly due to exposure to chronic low frequency noise originated from US Navy bombing. The study could not confirm the previous finding. Instead, a very small difference (0.15 mm) was identified and the pericardial thickness was normal in all subjects analyzed. However, when echocardiographic measurements were repeated by the Mayo Echo Core Lab, the pericardial measurements were thinner and no difference was found. The fact that the pericardial thickness was the only measurement with a small difference between two centers, the finding is most likely due to measurement variability intrinsic to echocardiography and measurement technique.

Moreover, there was no evidence from the echocardiographic examination that there was any cardiac pathology common to the study subjects. The Vieques residents should be reassured that there is no evidence from the Vieques Heart Study to indicate a clinically significant heart disease in them. The psychological stress and damage from the fear of having a heart disease is probably greater than any clinical consequence from 0.15 mm thicker pericardium obtained by echocardiography especially when the difference could not be confirmed by the Mayo Echo Core Lab.

Appendix E.10
Summary Statements Submitted by Participant #2

Study Design and Data Ascertainment:

The study was well designed to answer the question of whether or not a difference of greater than 1 mm thickness of the pericardium existed between the groups. I believe echocardiography would have been able to differentiate, or resolve, within this range (greater than 1mm) of pericardial thickness (clearly, a pericardium of 2 mm most likely is already accompanied by clinical signs of disease). Thus, from the standpoint of study design, I have no difficulty accepting the way that the study was written and conducted, and that it addressed the issue that had been raised by the preliminary results (Torres' study).

Echocardiographic Measurements:

The core laboratory at Mayo Clinic did an admirable job that is to be commended. A different issue is to try answer whether two groups of patients, one having a pericardium of 0.8 and the other a pericardium of 1.0 mm (mean thickness) could be distinguished, a range in which not only echocardiography, but even CT or MRI may not have the power to answer, conclusively, whether the two groups are different. The two laboratories (Mayo and the Ponce School of Medicine) must be congratulated in reaching agreement in the independent measurement of the data, except in the one instance where the instrument would not have permitted that agreement (less than 1mm thickness resolution).

Statistical Analysis:

Having said the above (i.e., having addressed the question on which the study was powered to answer), there were multiple other parameters of cardiac structure and function that were measured that can be useful from a public health standpoint to characterize the populations studied. This information may be very useful to the Department of Health in Puerto Rico to further evaluate the overall health conditions in Vieques in view of the data presented that shows a much higher incidence of stroke and heart disease as compared to the rest of Puerto Rico. Although the data analyzed and reported by the core laboratory at Mayo clinic concluded that there were no differences in the mean values of all the parameters when the populations of Ponce and Vieques were compared, some of the multivariate analysis of this data remains to be done.

As of today I am not convinced that there is no other information that can be gleaned or inferred from the results obtained that can help to say that the population of fishermen from Vieques is normal from the cardiovascular standpoint. Specifically, the significantly different mean age of the two populations (fishermen of Vieques 10 years younger, on average) mandates that several of the echocardiographic parameters, of which the normal values are known to be influenced by age, need to be analyzed in terms of their age-related distribution. More specifically, the parameters such as aortic root size, LV mass index, mitral deceleration time, mitral E-to-A ratio need to be expressed in terms of the subject's age in each group and then compared against the standard of a normal population available from Dr. Oh's reference values. In addition, LV end-diastolic dimension, LV posterior wall and septal thickness at end-diastole and calculated cardiac output need to be expressed (or corrected) in terms of the subject's weight, height and/or body mass index.

Interpretation and Inference:

In this context, the study is conclusive in saying that there are no pathologic changes in the pericardial thickness of the fishermen of Vieques. Additional analysis (multivariate, age-correction) needs to be done to further characterize the population of fishermen from Vieques before one can say that this is a "normal" population (and therefore, not different from the normal control group of fishermen from Ponce, or not different from normal individuals elsewhere).

Appendix E.11
Summary Statements Submitted by Participant #3

Study Design and Data Ascertainment:

- Sampling and study power were adequate to address Null hypothesis
- The nonresponse rate in Vieques reached 20% and we could not assess if the responders and nonresponders are different since nonresponder demographics were not studied
- Vieques fishermen were 10 years younger and age-adjustment was done
- Potential confounders were identified and found not to be significantly different among both populations

Echocardiographic Measurements:

- No gold standard used (echocardiogram is not the best instrument to use according to Core Lab)
- No case definition available (pericardial disease is non-specific)
- Measurements were not significantly different given fact that no thickness abnormalities were found by both groups
- Interobserver variability by Mayo group taken into account

Statistical Analysis:

- Statistical significance found by Ponce School of Medicine not confirmed by Mayo Core Lab
- Analysis of hemodynamic function did not identify statistically significant differences between study groups

Interpretation and Inference:

- Study groups are comparable

- With no case definition and no gold standard it is very difficult to interpret echocardiography findings when pericardial thickening is < 2mm
- As statistical significance attained by Ponce School of Medicine was not confirmed by Core Lab, there is no consistency of thickness findings
- Hemodynamic data points to no pathology consistent with no pericardial disease

Conclusions and Recommendations:

In a setting where we do not have a gold standard and a nonspecific case definition, it is very difficult to interpret results with the echocardiography instrument. The fact that the Core lab could not confirm the sponsor data points to inconsistency and weakens the initial statistically significant finding. The fact that the hemodynamic data parameters are consistent with no pathology leads me to believe that there is no difference between the two study groups with respect to pericardial thickening and pathology.