Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 7. Neural Control of breathing by a Signal Encoding Venous Pressure: Implication in Heart Failure

7. **Start and End Date of Research Project:** **7**/1/2010 - 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Philippe Haouzi, MD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 46,530

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
None			

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Haouzi Philippe	PI	25% Yr 1, 10% Yr 2, 10% 6 mos.
Harold Bell	Ass't Professor	10% Yr1, 10% Yr 2, 0% 6 mos.
Andry Van de Louw	Post Doc	10%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes____X_____ No_____

If yes, please indicate the source and amount of other funds:

The Department of Medicine supported salary and fringes for individuals named in item 9(C) - ~$107,000.

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the

application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Neural control of breathing by an afferent signal encoding	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (:AHA_)	January 2012	Grant in AID	Not awarded

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

We plan to resubmit a new Grant in Aid to the American Heart Association in January 2014

12. Future of Research Project. What are the future plans for this research project?

The results of the present study have shown that distension of the peripheral bed stimulates breathing. Our goal is to develop a chronic model in unanaesthetized sheep in which the inferior vena cava will be chronically occluded and to study the effect of vasoactive agents on the ventilatory response. The effects of blocking the afferent traffic coming from the muscle using cutaneous stimulation will be investigated.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				1
Female	2			
Unknown				
Total	**2**			**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	2			1
Unknown				
Total	**2**			**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				1
Black	2			
Asian				
Other				
Unknown				
Total	**2**			**1**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

    Yes____X_____ No_____

    If yes, please list the name and degree of each researcher and his/her previous affiliation:

    Dr. Andry Van de Louw, PhD, Universite Evry France

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

    Yes_____ No_____X_____

    If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. **Collaboration, business and community involvement.**

    16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

    Yes____X_____ No_____

If yes, please describe the collaborations:

Universite Henry Poincare France
Universite Evry, France

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16

months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Profound changes in the control of breathing accompany the syndrome known as 'heart failure' (HF). The mechanism(s) responsible for the excessive stimulation of breathing in HF which precipitate hypocapnia, Cheyne-Stokes breathing and dyspnea, are far from being understood. Given HF is a condition which affects millions of people in the United States, there is an urgent need for research which will aid in the development of effective therapies for treating or reducing the respiratory-related consequences of this disease state. Our research group has proposed that, in the absence of pulmonary oedema, the excessive ventilation that is observed in HF patients is caused by an increase in systemic venous pressure. My experiments will specifically determine whether an increase in systemic venous pressure leads to a stimulation of breathing, independently of changes occurring in the systemic pulmonary and systemic arterial circulation. I will also determine the mechanism through which breathing is stimulated. Using a novel, spontaneously breathing, anesthetized sheep preparation, I will employ a combination of venous occlusion and veno-venous shunt techniques in order to measure the ventilatory response to changes systemic venous pressure.

Specific Aim : To determine the magnitude of the increase in pulmonary ventilation caused specifically by an increase in pressure (load) in the systemic venous system. I will use a veno-venous circulatory bypass with a venous reservoir bag to isolate the contribution of increased venous pressure in the hind limb tissues, and determine the effects of the resulting increase in systemic venous pressure on ventilation. I predict that an increase in systemic venous pressure achieved only via increasing the load imposed upon venous return will stimulate breathing and lower $PaCO_2$. This part has been completed**.**

Main results

Introduction

We have developed a novel experimental model in spontaneously breathing, anaesthetized sheep which allows us to dissociate venous return from venous distension. The sheep were equipped with extracorporeal circuit comprising an external venous reservoir that allows independent control over the rate of venous return to the heart during the obstruction of the venous outflow from the hindlimbs (figure 1).

Methodological Basis

1- *Partial extracorporeal circulation:*

The extracorporeal circuit is presented in Figure 1. The circuit connected the inferior and superior vena cava (IVC and SVC, respectively) via 2 pumps with a large venous reservoir bag (3 liters) interposed between the pumps. Pump 1 withdrew blood from the inferior vena cava to the reservoir bag and pump 2 reinjected the blood at the same rate. The circuit was primed with a solution containing heparin before any data collection is performed. An intravenous occlusion catheter was placed in the IVC to obstruct venous outflow and create a distension of the hindlimb circulation. The protocol applied is the one presented in the project.

Nine sheep have been studied. Out of the 9 animals studied, data from 7 sheep could be analyzed:

Change in Venous Return without distending the Peripheral Venous System (no venous distension and low cardiac output)
As shown on figure 2, reducing venous return was obtained by stopping pump 2. The effects were a reduction in venous return to the heart, a decrease in blood pressure and an increase in the volume of blood in the reservoir bag. We found that there was very little effect on breathing as we have previously reported. In some cases ventilation actually dropped but the changes in ventilation were not significant (-8 %±12 from baseline). End tidal PCO2 decreased by 12±4 Torr reflecting the reduction in venous return. Restoring venous return restored arterial blood pressure.

Peripheral Venous Distension (venous obstruction) with low venous return (venous distension and low cardiac output)
The pumps (P1 and P2) were stopped while the IVC was occluded. In all instances breathing started to rise progressively by 65± 8 % (Figure 2). End tidal CO2 dropped. In other words, for a reduction in blood pressure similar to condition 1, ventilation was systematically stimulated when the venous system was distended.

Peripheral Venous Distension (venous obstruction) while restoring venous return (venous distension and "normal" cardiac output)
When Pump (P2) was allowed to restore venous return while pump 1 was stopped and IVC was occluded, ventilation decreased to baseline (figure 2).

Peripheral Venous Distension while increasing central venous return to the heart (venous distension and high cardiac output)
Figure 3 illustrates the effects of venous occlusion in the condition of very high venous return. This condition resulted in all instances in a stimulation of breathing which averaged 153±27%, along with a reduction in end tidal CO2.

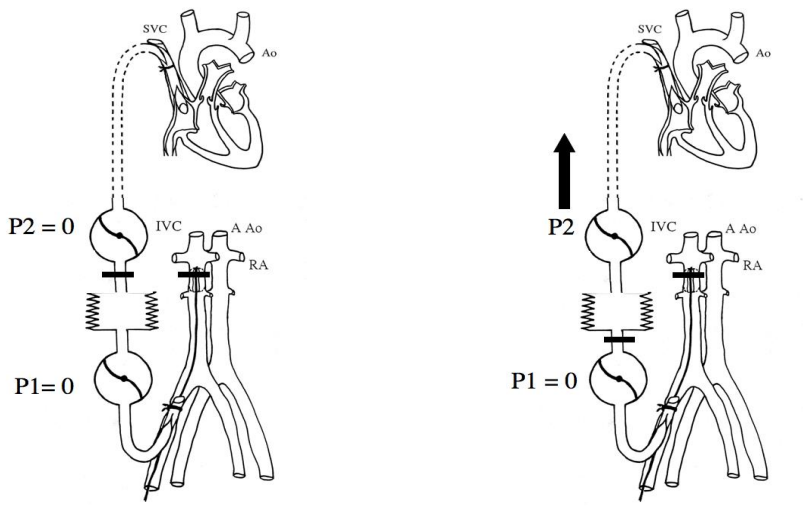

Figure 1:Schematic representation of the model where the inferior vena cava (IVC) was occluded. The reservoir bag contains venous blood at the same composition as the blood returning from the hindlimb circulation. During the occlusion of the inferior vena cava, the flow of blood from pump 2 (P2) was adjusted so that cardiac output will lower *Left panel (P2 was stopped), the same or higher than in baseline conditions* (*Right panel).*

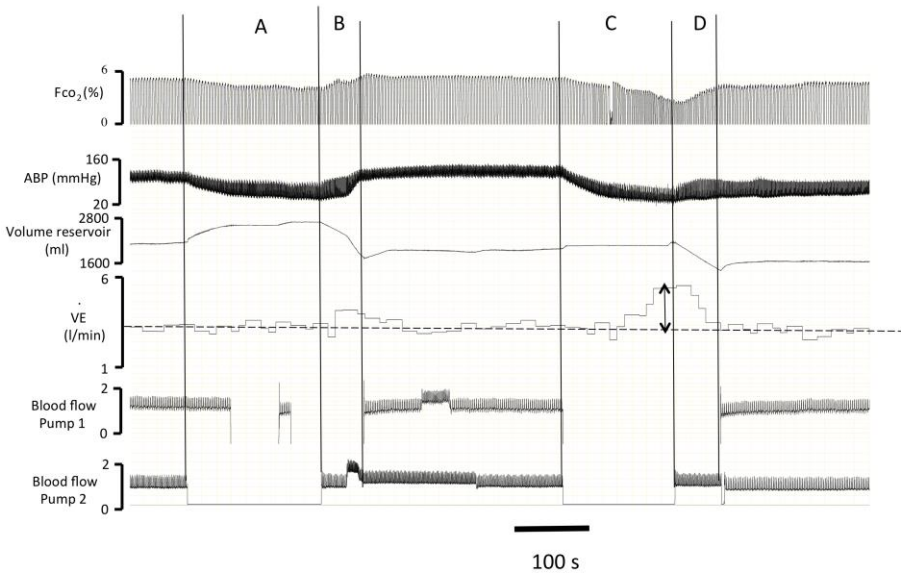

Figure 2: **A** Responses to the reduction in venous return. Pump 2 was stopped, as pump 1 was still working venous return decreased, leading to a decrease in cardiac output and blood pressure (ABP). Minute ventilation (VE) did not change in this example. **B** Venous return was restored. **C** The vena cava was occluded while pump 1 and 2 were stopped. ABP decreased just like in condition A, but ventilation was progressively stimulated. Restoring venous return in **D** decreased ventilation to baseline levels.

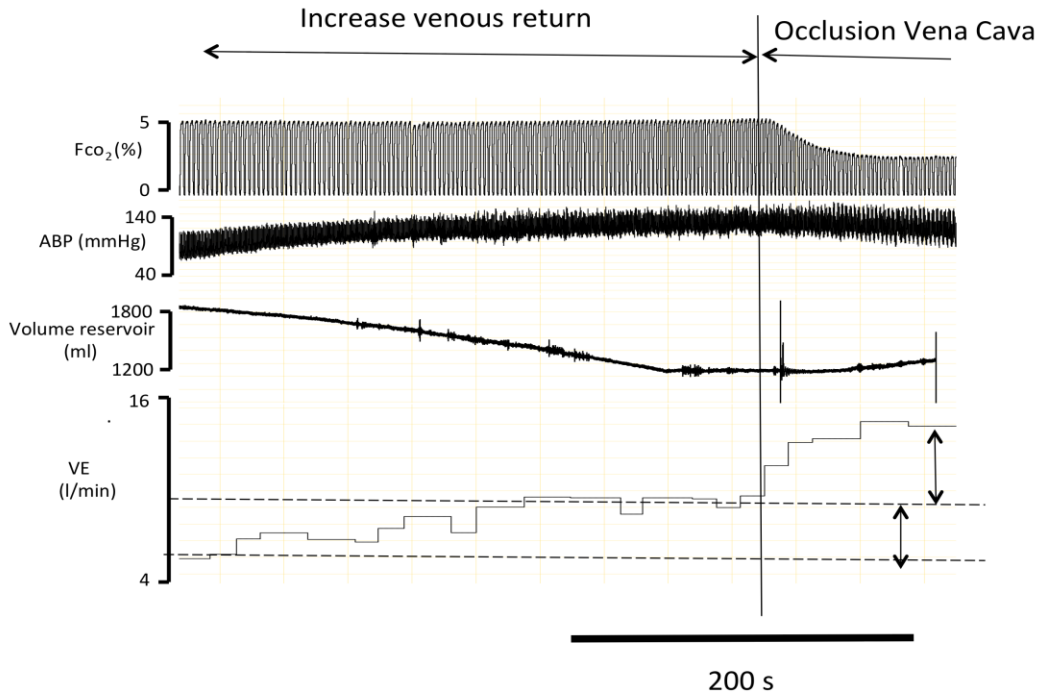

Figure 3: Venous return was increased by about 50 % of baseline (decrease in the volume of the reservoir bag), ventilation was stimulated. Occluding the vena cava produced an additional rapid and large increase in ventilation

2- *Total extracorporeal circulation (arterio-venous shunt connected to an oxygenator (Terrumo), wherein venous return was manipulated without involving cardiac or lung receptors.*

This approach allowed us to study the effects of Venous distension during complete extracorporeal circulation and cardiac arrest (ventricular fibrillation).

These data have been obtained in 3 sheep by maintaining the animals in complete extracorporeal circulation while the heart was stopped (ventricular fibrillation or hyperkalemia). In this condition, the circuit was venous-arterial while the reservoir bag could maintain enough blood flow for 2-3 minutes whenever venous return was blocked. The volume of the reservoir bag gives therefore a reverse image of the distension of the entire venous system. In all instances, decreasing venous return resulted (in turn increasing venous distension) in an increase in systemic blood pressure (increase peripheral resistance, see figure 4 below). This phenomenon was exacerbated during hindlimb contractions.

In addition to our previous results demonstrating that there is a genuine stimulation of breathing triggered by peripheral venous distension which interacts with the stimulation of other receptors

located in the central circulation when venous return increases changes, we found that blood pressure was also increased through the same mechanism.

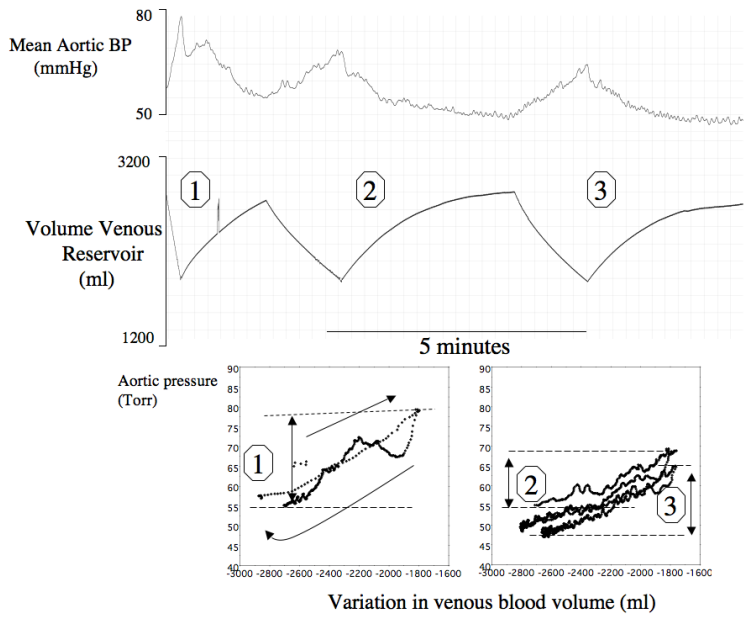

Figure 4 Changes in Mean aortic pressure when Venous return was impeded in an animal under complete cardio-pulmonary bypass while the heart was stopped. The change in blood volume in the reservoir bag is the reverse image of the change in venous volume. Note the increase in aortic pressure when venous volume increases.

Our results are showing that there is a genuine stimulation of breathing triggered by peripheral venous distension regardless of the stimulation of other receptors located in the central circulation when venous return increases changes. The conditions created by these models are aimed at mimicking some of the elementary changes in hemodynamic changes in right sided or global heart failure. When venous return was restored along with venous distension, ventilation returned to baseline. Conditions of high venous return produced an abrupt increase in breathing when associated with venous distension.

Future direction:

1- The next step will be to investigate the mechanism through which an increase in systemic venous pressure causes an excessive level of pulmonary ventilation. These experiments will directly test the hypothesis that the stimulation of breathing which results from an increase in systemic venous pressure arises from a stimulation of mechanosensitive afferents in the muscle tissue that respond to changes in vascular distension. Infusions of various agents into the hind limbs will be used to block the activation of mechanogated ion channels on group III and IV muscle afferents and transient receptor potential vanilloid receptors.

2- A unique observation was made which led to a new study, indeed a very important and unexpected phenomenon was described during the experiments wherein the animal was in total extracorporeal circulation (heart was stopped) at rest or during muscle contractions. The results on the persistence of eupneic breathing during a cardiac arrest following exercise have been reported in the following publication:
Breathing during cardiac arrest following exercise: a new function of the respiratory system? Haouzi P, Van De Louw A, Haouzi A. Respir Physiol Neurobiol. 2012;181(2):220-7).
This publication is the extension of the direct preliminary experiments we have obtained using the model presented in this report.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?
___ __Yes
___X_No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?
_____Yes
__X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility

criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
____Yes
____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Breathing during cardiac arrest following exercise: a new function of the respiratory system?	**Haouzi P**, Van De Louw A, Haouzi A. PubMed	Respir Physiol Neurobiol.	March 2012	☐Submitted ☐Accepted XPublished

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____X___ No_____

If yes, please describe your plans:

Studies on the effects of vasoactive agents on breathing control are currently being performed.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None. The study is a physiological study aimed at understanding and then possibly treating the respiratory changes occurring in cardiac failure.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

As mentioned in the previous paragraph, these studies led to unexpected results on breathing control during cardiac arrest. Although these data have implication beyond patients in heart failure, they triggered a new field of investigation that led to a publication.
Important information for the public:

1- Using breathing as a criteria for cardiac arrest is misleading.
2- The persistence of breathing during a cardiac arrest is proportional to the level of metabolism preceding the cardiac arrest. This has important implication for the CPR strategies.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in

the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No __
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

NAME **Haouzi, Philippe A.**	POSITION TITLE Professor of Medicine, Penn State University College of Medicine
eRA COMMONS USER NAME phaouzi	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Lycée Henri Poincaré (Nancy, France)	Baccalaureat	06/1977	Mathematics
Faculté de Médecine de Nancy (France)	MD	09/1978-08/1983	Medical study
Centre Hospitalo-Univesitaire de Nancy		09/1980-08/1983	Residency
Hôpital Kremlin Bicêtre (Assistance publique des hôpitaux de Paris) (France)	Fellowship	09/1983-09/1987	Pediatric Intensive Care Adult Pulmonary Medicine Physiology
Doctorat de L'université H.Poincaré et Institut Polytechnique de Lorraine (France)	Ph.D.	09/1994	

A. **Positions and Honors**

Professional Experience

1988 - 1991 Assistant Professor of Medicine and Physiology, Université H. Poincaré, Nancy, Faculté de Médecine de Nancy, France, University Hospital of Nancy, France.

1990 - 1991 Research Fellow, Harbor UCLA Medical Center, University of California, Los Angeles, Torrance, California, USA.

1991 - 1996 Associate Professor of Medicine and Physiology, Université H. Poincaré, Faculté de Médecine de Nancy, France. Children Hospital, University Hospital of Nancy, France.

1997 - 1997 Visiting Professor, University California Davis, Davis, USA

2002 - 2007 Chief, Divison of Pulmonary Function Testing and Exercise Lab, University Hospital of Nancy, France.

2000 - 2007 Director, Research Group EA 4350, Université H. Poincaré, Faculté de Médecine Nancy, Laboratoire de Physiologie, de Nancy.

1996 - 2007 Professor of Medicine and Physiology, Université H. Poincaré, Nancy, Faculté de Médecine de Nancy, France.

2007 - present Professor of Medicine, Heart and vascular Institute, Division of Pulmonary and Critical Care Medicine, Pennsylvania State University College of Medicine, Hershey, PA,

Honors and Awards

- Grant (principal investigator) from the Regional Medical Research Foundation "Lorraine" (1990)
- Award and fellowship from the French Society of Pediatric Research (1990)

- Fellowship from the Philippe Foundation, New-York (1990)
- One year grant (principal investigator) from the French Medical Research Foundation (1993)
- One year grant (principal investigator) from INSERM, Research Career Development Award (1993)
- One year grant (principal investigator) for clinical research, contract with the University Hospital of Nancy / Contrat de Programme de Recherche Clinique, CHU Nancy (1994)
- Bourse OTAN (NATO fellowship) for senior scientist, (1997)
- Four year grant (principal investigator) from the French Ministry of Science (contract EA 3450 2000-2004)
- Fellowship from the Japanese Society for the Promotion of Science (JSPS) Invited lectures in Japan and research program on the regulation of respiration (2002).
- Lauréat de l'Académie Nationale de Médecine (French Academy of Medicine) (2003).
- Four year grant (principal investigator) from the French Ministry of Science (contract EA 3450 2005-2009)

Service

- Elected member of the Medical Board of the University Hospital of Nancy, France *(2003-2007)*
- Elected member of the Scientific Committee of the University Henry Poincare, France (1994-2001)
- Elected member of the Teaching Committee of the University Henry Poincare, France (1994-2001)
- Elected member of 'la Société Française de Physiologie' (since 1993)
- Member of the American Physiological Society (since 1995)
- Member of the American Thoracic Society
- Referee: *Journal of Applied Physiology, European Journal of Applied Physiology, American Journal of Physiology, Respiratory Physiology and Neurobiology, Pediatric research, Canadian journal of Applied Physiology, Experimental Physiology, Critical Care Medicine, Chest.*

C. Selected Peer-Reviewed Publications (Selected from 76 peer-reviewed publications)

Most relevant to the current application

1. Klingerman CM, Trushin N, Prokopczyk B, **Haouzi P.** H2S concentrations in the arterial blood during H2S administration in relation to its toxicity and effects on breathing. *Am J Physiol Regul Integr Comp Physiol*. 2013 Jul 31. [Epub ahead of print] PMID: 23904109; PMCID: PMC3763045.
2. **Haouzi P**, Klingerman CM. Fate of intracellular H2S/HS^- and metallo-proteins. *Respir Physiol Neurobiol*. 2013;188(2):229-30. PubMed PMID: 23748103.
3. Van de Louw A, **Haouzi P.** Ferric Iron and Cobalt (III) compounds to safely decrease hydrogen sulfide in the body? *Antioxid Redox Signal.* 2013, 19(5):510-6. PubMed PMID:22233239.
4. **Haouzi P,** Bell H, Van de Louw A. Hypoxia-induced arterial chemoreceptor stimulation and hydrogen sulfide: too much or too little? *Respir Physiol Neurobiol.* 2011;179(2-3):97-102. PMID: 22001444.

5. **Haouzi P**, Bell HJ, Notet V, Bihain B. Comparison of the metabolic and ventilatory response to hypoxia and H_2S in unsedated mice and rats. *Respir Physiol Neurobiol*. 2009;167(3:316-22. PMID: 19539788.

Additional publications of importance to the field

6. **Haouzi P**, Van de Louw A. Uncoupling mitochondrial activity maintains body VO2 during hemorrhage-induced O2 deficit in the anesthetized rat. *Respir Physiol Neurobiol.* 2013;186(1):87-94. PMID: 23333818.
7. Van de Louw A, **Haouzi P**. Oxygen deficit and H2S in hemorrhagic shock in rats. *Crit Care*. 2012 Oct 2;16(5):R178. PMID: 23031430; PMCID: PMC3682279.
8. **Haouzi P.** Murine models in critical care research. *Crit Care Med*. 2011; 39(10): 2290-3.PMID: 21666454
9. **Haouzi P**, Bell H, Philmon M. Hydrogen sulfide oxidation and the arterial chemoreflex: effect of methemoglobin. *Respir Physiol Neurobiol.* 2011;177(3):273-83. PMID: 21569867.
10. **Haouzi P**, Ahmadpour N, Bell HJ, Artman S, Banchs J, Samii S, Gonzalez M, Gleeson K. Breathing patterns during cardiac arrest. *J Appl Physiol.* 2010;109(2):405-11. PMID: 20489033.
11. Tiangco D, **Haouzi P**. Breathing requirement and metabolic rate during cardiopulmonary resuscitation: cardiac arrest during exercise. *Crit Care Med.* 2010; 38(8):1760-1. PubMed PMID: 20647817.
12. **Haouzi P.** Ventilatory and metabolic effects of exogenous hydrogen sulfide. *Respir Physiol Neurobiol.* 2012 ;184(2):170-7.PubMed PMID: 22579639.
13. Bell HJ, **Haouzi P**. Acetazolamide suppresses the prevalence of augmented breaths during exposure to hypoxia. *Am J Physiol Regul Integr Comp Physiol*. 2009 297(2):R370-8. PMID: 19494178.
14. Bell HJ, Ferguson C, Kehoe V, **Haouzi P.** Hypocapnia increases the prevalence of hypoxia-induced augmented breaths. *Am J Physiol Regul Integr Comp Physiol.* 2009; 296(2):R334-44. PubMed PMID: 19091914.
15. **Haouzi P,** Notet V, Chenuel B, Chalon B, Sponne I, Ogier V, Bihain B. H2S induced hypometabolism in mice is missing in sedated sheep. *Respir Physiol Neurobiol.* 2008;160(1):109-15. PMID: 17980679.

D. Research Support

Ongoing Research Support.

NIH: 1R21NS080788-01 Haouzi (PI) 10/01/2012-10/01/2014
Title: Crystalline hydroxocobalamin and methemoglobin as a treatment of H2S intoxication"
Role PI

Completed Research Support since 2008

Resubmission Development Grant (PA) RFA Number 08-07-06 Haouzi (PI) 06/01/2010 - 06/01/2012
Sponsor: Pennsylvania State Department of Health
Title: Peripheral circulation and control of breathing
Role: PI

Dean's Feasibility Grant Haouzi (PI) 01/07/2008 – 06/30/2009
Penn State University
Title: Systemic Venous Pressure as a Determinant of Respiration. Penn State University
Role: PI

EA 3450 2005-2009 Haouzi (PI) 01/07/ 2005 - 01/07/2009
French Ministry of Research
Title: Interaction between the control of breathing and circulation.
Role: PI

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Bell, Harold James	Assistant Professor of Medicine and Cellular and Molecular Physiology
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Innis College, University of Toronto, Canada	B.SC.(Hon)	1997	Human Physiology
Dept. of Physiology, University of Toronto, Canada	M.Sc.	2000	Respiratory Physiology
Dept. of Physiology, University of Toronto, Canada	Ph.D.	2005	Respiratory Physiology
Hotchkiss Brain Institute, Univ. of Calgary, Canada	Postdoc	2007	Respiratory Neurophysiology
Penn State Univ. College of Med., Hershey, PA, USA	Postdoc	2009	Respiratory Physiology

A. Positions and Honors.

Positions and Employment

2009 – pres Assistant Professor, Penn State University College of Medicine, Hershey, PA, USA

Professional Memberships and Service

2010 – pres Member, Graduate Faculty, Pennsylvania State University
2010 – pres Ad Hoc reviewer, Discovery Grants section, Natural Sciences and Engineering Research Council of Canada (NSERC)
2010 – pres Guest Editor, Methods Series Frontiers Reviews, Resp Physiol Neurobiol
2008 – pres Editorial Board Member, Respiratory Physiology and Neurobiology
2005 – pres Member, Society for Neuroscience
2003 – pres Member, American Physiological Society, Respiration & Envir. Physiology sections

Other Professional Service

Ad-hoc reviewer for the following peer -reviewed scientific journals:
Acta Physiologica
American Journal of Physiology - Regulatory, Integrative, Comparative Physiology
American Journal of Respiratory and Critical Care Medicine
Applied Physiology, Nutrition and Metabolism
Journal of Physiology
European Journal of Applied Physiology
Physiological Genomics
Journal of Applied Physiology
Journal of Neurophysiology
Journal of Physiology
Respiration Physiology and Neurobiology

Honors

2006 - Young Investigator Award, Xth Oxford Conference on Modeling and Control of Breathing ($800)
2005 - Fellowship, Alberta Heritage Foundation for Medical Research, ($114,000/3 yrs)
2003 - Scholarship, Faculty of Medicine, University of Toronto (Sept - $9 600)
2003 - Scholarship, Faculty of Medicine, University of Toronto (Jan - $8 000)
2002 - Scholarship, Faculty of Medicine, University of Toronto, ($19 300)

B. Peer-reviewed publications *(limited to 15 most relevant)*

1. **Bell HJ**, Ramsaroop D, Duffin J (2003) The respiratory effects of two modes of passive exercise. Eur J Appl Physiol. 88(6): 544-52.
2. **Bell HJ**, Duffin J. (2003) CO_2 does not affect passive exercise ventilatory decline. J Appl Physiol. 95(1):322-9.
3. **Bell HJ**, Duffin J. (2004) The respiratory response to passive limb movement is suppressed by a cognitive task. J Appl Physiol. 97(6):2112-20.
4. **Bell HJ**, Feenstra W, Duffin J. (2005) The initial phase of exercise hyperpnoea in humans is depressed during a cognitive task. Exp Physiol. 90(3):357-65.
5. **Bell HJ**, Duffin J. (2006) Rapid increases in ventilation accompany the transition from passive to active movement. Respir Physiol Neurobiol. 152(2):128-42.
6. **Bell HJ**. (2006) Respiratory control at exercise onset: an integrated systems perspective. Respir Physiol Neurobiol. 152(1):1-15
7. **Bell HJ**, Inoue T, Shum K, Luk C, Syed NI. (2007) Hypoxia-induced plasticity of synaptic connections between oxygen-sensitive cells and the respiratory central pattern generator. Eur J Neurosci. 25: 3537-50.
8. **Bell HJ**, Syed NI. (2009) Hypoxia-induced modulation of the respiratory CPG. Front Biosci. 14:3825-35.
9. Haouzi P, **Bell HJ**. (2009) Control of breathing and voluntary respiratory rhythm in humans. J Appl Physiol. 106(3):904-10.
10. **Bell HJ**, Ferguson C, Kehoe V and Haouzi P. (2009) Hypocapnia increases the prevalence of hypoxia induced augmented breaths. Am J Physiol Regul Integr Comp Physiol. 297(2):R370-81.
11. Haouzi P, **Bell HJ**, Notet V, Bihain B. (2009) Comparison of the metabolic and ventilatory response to hypoxia and H_2S in unsedated mice and rats. Respir Physiol Neurobiol. 31;167(3):316-22.
12. Bekteshi E, **Bell HJ**, Haouzi A, El-Banayosy A, Haouzi P. (2010) Control of breathing during acute change in cardiac preload in a patient with partial cardiopulmonary bypass. Respir Physiol Neurobiol. 31;170(1):37-43.
13. **Bell HJ**, Haouzi P. (2010) The hypoxia-induced facilitation of augmented breaths is suppressed by the common effect of carbonic anhydrase inhibition. Respir Physiol Neurobiol. 31;171(3):201-11.
14. Haouzi P, **Bell HJ**. (2010) Respiratory effects of changing the volume load imposed on the peripheral venous system. Respir Physiol Neurobiol. 31;171(3):175-80.
15. Haouzi P, Ahmadpour N, **Bell HJ**, Artman S, Banchs J, Samii S, Gonzalez M, Gleeson K. (2010) Breathing patterns during cardiac arrest. J Appl Physiol. 109(2):405-11.