Publications related to Appendix 8

The following lists of citations are provided to the committee in response to the request that we received, asking for “all papers associated with” the currently active IACUC-approved VA research protocols with dogs. Some of these citations have already been provided to the committee in other contexts, but are included again here to show how they fit into the literature related to these protocols. The focus in these lists is on peer-reviewed full-length publications related to each of the protocols that were listed in Appendix 8 as approved for continuation as of March 28, 2018, and still open as of November 15, 2018. The most recent reports of research are usually in the form of abstracts that are published as summaries of results that are presented orally or in poster presentations at scientific conferences. Abstracts may also be peer-reviewed, but contain only summary information, so are not included here.

It is important to note that these lists cannot be considered complete, because the nature of scientific discovery is always to build on what has been learned and reported before, which in turn was built on what was learned and reported before that, so that the work done for each piece of the puzzle is “associated” with a large network of previous publications. And each publication stimulates new research to answer questions that arise from the new knowledge, so each piece of the puzzle will also become “associated” with a large network of future publications. The lists provided are also limited because of constraints on the time and resources available to assemble the lists, and must be recognized as only the results of our best efforts to date. Many publications have certainly been omitted, and those omissions should not be interpreted as signifying anything other than the limits of our efforts. Each of these citations represents another “piece of the puzzle” that the currently active research is designed to contribute to. Each publication also contains a list of further citations of relevant publications.

The current research may be very similar to the work reported in some of the publications cited here, involving the same models, and procedures, carried out by the same or different investigators, with or without VA support. Such publications show the value of the models used. The current research builds on the findings of such earlier work by (1) establishing how reproducible and representative of reality the earlier findings were, and then (2) expanding on those earlier findings or building on them to put in the next piece of the puzzle. Publications in this category may be thought of as puzzle pieces that the currently active research is designed to fit directly into.

The current research may also appear to be very different from the work reported in others of the publications cited, involving different models and procedures, carried out by different investigators focused on different parts of the larger puzzle. Such work may appear to be only indirectly or tangentially related to the current research, but is nonetheless part of the foundation on which the current work is built. Publications in this category may be thought of as puzzle pieces that are more distant from the focus of the current work, but are nonetheless essential for holding in place the pieces that the currently active research is designed to fit directly into.
Because rigorous biomedical research requires very careful definition of terms, closely drawn distinctions among similar concepts, and painstaking analysis and interpretation, it is important to take precautions against getting misled by similarities or differences in the titles of protocols and publications, which are intentionally simplified and cannot fully convey all of those detailed nuances. To recognize how each publication or protocol fits into the puzzle, it is necessary to read the full document closely.

Protocols that address different aspects of very similar topics (adjacent portions of the puzzle), such as the protocols at Richmond, must be based on similar background knowledge, so it is expected that there will be overlap among even the most recent and closely associated publications cited for each of these related protocols.

*Explanatory notes are provided in italics.*
Protocol Title: High Frequency Spinal Cord Stimulation to Restore Cough
VA Station: Cleveland
Status of research with dogs: approved, work with dogs is ongoing

(Citations are listed with the most recent publications first.)


   This report documents the feasibility of using a mechanism developed through research with dogs, to restore expiratory function in human subjects with spinal cord injury. The current research is designed to improve on the mechanism reported here, by developing ways to use lower voltage that is applied more selectively, so as to minimize side effects.


11. DiMarco AF, Kowalski KE. Distribution of electrical activation to the external intercostal muscles during


This investigator was granted permission by the FDA to conduct components of this project than can be done with human subjects, and so has elected to focus on those aspects of the project at this time, leaving the work with dogs for later. Most medical advances are made not through a neatly unidirectional process, but as the result of many iterative cycles, to understand the underlying physiology and pathology, to develop methods of intervening to alter pathological development and to facilitate recovery of health (which often yields further insights into the underlying physiology and pathology, and informs further development of the interventions), and to refine those methods for safe clinical application (which often also yields further insights into the underlying physiology and pathology, and makes further refinement of the interventions possible). This means that it is unremarkable that some aspects of the research may be most appropriately conducted with human subjects, while other components yet to be carried out must still be done with dogs.
Protocol Title: Contribution of Inflammation and Oxidative Stress in Pericardial Fluid to Postoperative Atrial Fibrillation after Cardiac Surgery
VA Station: St. Louis
Status of research with dogs: approved, work with dogs has not yet started

*The current gold standard for the surgical treatment of atrial fibrillation was based on extensive research that was all done with dogs, including that listed as accomplishment 25 in Appendix 6. The current protocol in Appendix 8 will continue this line of research, to more fully understand and manage atrial fibrillation. The list of publications provided below gives some idea of the many pieces of the puzzle that these investigators have put into place. (Citations are listed with the most recent publications first.)*

The hemodynamic and atrial electrophysiologic consequences of chronic left atrial volume overload in a controllable canine model

**Postoperative atrial fibrillation: The role of the inflammatory response.**
Ishii Y, Schuessler RB, Gaynor SL, Hames K, Damiano RJ Jr.

Local transmural action potential gradients are absent in the isolated, intact dog heart but present in the corresponding coronary-perfused wedge.
Boukens BJ, Meijborg VMF, Belterman CN, Opthof T, Janse MJ, Schuessler RB, Coronel R, Efimov IR.

**The Electrophysiologic Effects of Acute Mitral Regurgitation in a Canine Model.**

Proteomic Profiling of Early Chronic Pulmonary Hypertension: Evidence for Both Adaptive and Maladaptive Pathology.
Aziz A, Lee AM, Ufere NN, Damiano RJ, Townsend RR, Moon MR.
J Pulm Respir Med. 2015;5(1). pii: 1000241

Multistage electrotherapy delivered through chronically-implanted leads terminates atrial fibrillation with lower energy than a single biphasic shock.
Janardhan AH, Gutbrod SR, Li W, Lang D, Schuessler RB, Efimov IR.

**Heterogeneity and function of K(ATS) channels in canine hearts.**

Impact of differential right-to-left shunting on systemic perfusion in pulmonary arterial hypertension.
A novel low-energy electrotherapy that terminates ventricular tachycardia with lower energy than a biphasic shock when antitachycardia pacing fails.
Janardhan AH, Li W, Fedorov VV, Yeung M, Wallendorf MJ, Schuessler RB, Efimov IR.

The effects of inflammation on heart rate and rhythm in a canine model of cardiac surgery.

Complex interactions between the sinoatrial node and atrium during reentrant arrhythmias in the canine heart.
Fedorov VV, Chang R, Glukhov AV, Kostecki G, Janks D, Schuessler RB, Efimov IR.

Vagal denervation and reinnervation after ablation of ganglionated plexi.

Structural and functional evidence for discrete exit pathways that connect the canine sinoatrial node and atria.

Interatrial shunt for chronic pulmonary hypertension: differential impact of low-flow vs. high-flow shunting.
Zierer A, Melby SJ, Voeller RK, Moon MR.

Impact of calcium-channel blockers on right heart function in a controlled model of chronic pulmonary hypertension.
Zierer A, Voeller RK, Melby SJ, Steendijk P, Moon MR.

Atrial fibrillation propagates through gaps in ablation lines: implications for ablative treatment of atrial fibrillation.

Pulmonary vein isolation and the Cox maze procedure only partially denervate the atrium.
Lall SC, Foyil KV, Sakamoto S, Voeller RK, Boineau JP, Damiano RJ Jr, Schuessler RB.
Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis.

Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation.

Physiological consequences of bipolar radiofrequency energy on the atria and pulmonary veins: a chronic animal study.
Prasad SM, Maniar HS, Diodato MD, Schuessler RB, Damiano RJ Jr.

Cryoablation of ventricular tachycardia guided by return cycle mapping after entrainment.
Nitta T, Mitsuno M, Rokkas CK, Lee R, Schuessler RB, Boineau JP.

Spatial distribution and frequency dependence of arrhythmogenic vagal effects in canine atria.
Sharifov OF, Zaitsev AV, Rosenshtraukh LV, Kaliadin AY, Beloshapko GG, Yushmanova AV, Schuessler RB, Boineau JP.
J Cardiovasc Electrophysiol. 2000 Sep;11(9):1029-42.

Effects of measurement error and sampling resolution on estimates of atrial tissue recovery parameters.
Kay MW, Bayly PV, Schuessler RB.

Use of the voice-controlled and computer-assisted surgical system ZEUS for endoscopic coronary artery bypass grafting.

The closed heart MAZE: a nonbypass surgical technique.
Lee R, Nitta T, Schuessler RB, Johnson DC, Boineau JP, Cox JL.

Radial approach: a new concept in surgical treatment for atrial fibrillation. II. Electrophysiologic effects and atrial contribution to ventricular filling.

Nontransmural laser treatment incompletely denervates canine myocardium.
Kwong KF, Schuessler RB, Kanellopoulos GK, Saffitz JE, Sundt TM 3rd.
A canine model of atrial flutter following the intra-atrial lateral tunnel Fontan operation.
Bromberg BI, Schuessler RB, Gandhi SK, Rodefeld MD, Boineau JP, Huddleston CB.

Differential expression of gap junction proteins in the canine sinus node.
Kwong KF, Schuessler RB, Green KG, Laing JG, Beyer EC, Boineau JP, Saffitz JE.

Return cycle mapping after entrainment of ventricular tachycardia.
Nitta T, Schuessler RB, Mitsuno M, Rokkas CK, Isobe F, Cronin CS, Cox JL, Boineau JP.

Varying types of circus movement re-entry with both normal and dissociated contralateral conduction causing different right and left atrial rhythms in canine atrial flutter.
Yamauchi S, Boineau JP, Schuessler RB, Cox JL.

Transmyocardial laser treatment denervates canine myocardium.

Spontaneous atrial flutter in a chronic canine model of the modified Fontan operation.
Gandhi SK, Bromberg BI, Rodefeld MD, Schuessler RB, Boineau JP, Cox JL, Huddleston CB.

Structural determinants of slow conduction in the canine sinus node.
Saffitz JE, Green KG, Schuessler RB.

Spatial coherence: a new method of quantifying myocardial electrical organization using multichannel epicardial electrograms.
Fendelander L, Hsia PW, Damiano RJ Jr.

Relationship between local atrial fibrillation interval and refractory period in the isolated canine atrium.
Kim KB, Rodefeld MD, Schuessler RB, Cox JL, Boineau JP.
Circulation. 1996 Dec 1;94(11):2961-7.

Improved nonthoracotomy defibrillation based on ventricular fibrillation waveform characteristics.
Left-sided atrial flutter: characterization of a novel complication of pediatric lung transplantation in an acute canine model.
Gandhi SK, Bromberg BI, Schuessler RB, Boineau JP, Cox JL, Huddleston CB.

Anatomically based ablation of atrial flutter in an acute canine model of the modified Fontan operation.
Rodefeld MD, Gandhi SK, Huddleston CB, Turken BJ, Schuessler RB, Boineau JP, Cox JL, Bromberg BI.

Characterization and surgical ablation of atrial flutter after the classic Fontan repair.
Gandhi SK, Bromberg BI, Schuessler RB, Turken BJ, Boineau JP, Cox JL, Huddleston CB.

Lateral tunnel suture line variation reduces atrial flutter after the modified Fontan operation.
Gandhi SK, Bromberg BI, Rodefeld MD, Schuessler RB, Boineau JP, Cox JL, Huddleston CB.

A critical period of ventricular fibrillation more susceptible to defibrillation: real-time waveform analysis using a single ECG lead.

Atrial flutter after lateral tunnel construction in the modified Fontan operation: a canine model.
Rodefeld MD, Bromberg BI, Schuessler RB, Boineau JP, Cox JL, Huddleston CB.

Defibrillation success is associated with myocardial organization. Spatial coherence as a new method of quantifying the electrical organization of the heart.
Hsia PW, Fendelander L, Harrington G, Damiano RJ.

Relative densities of muscarinic cholinergic and beta-adrenergic receptors in the canine sinoatrial node and their relation to sites of pacemaker activity.
Beau SL, Hand DE, Schuessler RB, Bromberg BI, Kwon B, Boineau JP, Saffitz JE.

Primary negativity does not predict dominant pacemaker location: implications for sinoatrial conduction.
Bromberg BI, Hand DE, Schuessler RB, Boineau JP.

Anterior septal coronary artery infarction in the canine: a model of ventricular tachycardia with a subendocardial origin. Ablation and activation sequence mapping.
Tweddell JS, Rokkas CK, Harada A, Pirolo JS, Branham BH, Schuessler RB, Boineau JP, Cox JL.
Integration of absolute ventricular fibrillation voltage correlates with successful defibrillation.

Characterization and surgical ablation of acute atrial flutter following the Mustard procedure. A canine model.
Cronin CS, Nitta T, Mitsuno M, Isobe F, Schuessler RB, Boineau JP, Cox JL.

Use of intraoperative mapping to optimize surgical ablation of atrial flutter.
Yamauchi S, Schuessler RB, Kawamoto T, Shuman TA, Boineau JP, Cox JL.

Simultaneous epicardial and endocardial activation sequence mapping in the isolated canine right atrium.
Schuessler RB, Kawamoto T, Hand DE, Mitsuno M, Bromberg BI, Cox JL, Boineau JP.

Lessons learned from computerized mapping of the atrium. Surgery for atrial fibrillation and atrial flutter.
Ferguson TB Jr, Schuessler RB, Hand DE, Boineau JP, Cox JL.

Cholinergically mediated tachyarrhythmias induced by a single extrastimulus in the isolated canine right atrium.
Schuessler RB, Grayson TM, Bromberg BI, Cox JL, Boineau JP.

The effect of augmented atrial hypothermia on atrial refractory period, conduction, and atrial flutter/fibrillation in the canine heart.
Sato S, Yamauchi S, Schuessler RB, Boineau JP, Matsunaga Y, Cox JL.

Significant left ventricular contribution to right ventricular systolic function.
Damiano RJ Jr, La Follette P Jr, Cox JL, Lowe JE, Santamore WP.

Spontaneous tachyarrhythmias after cholinergic suppression in the isolated perfused canine right atrium.
Schuessler RB, Rosenshtraukh LV, Boineau JP, Bromberg BI, Cox JL.

Feasibility of closed heart discrete cryomodification of atrioventricular conduction. Electrophysiologic effects in the canine heart.
Yagi Y, Schuessler RB, Boineau JP, Cox JL.
The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure.

The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation.
Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP.

Functional consequences of the right ventricular isolation procedure.
Damiano RJ Jr, Asano T, Smith PK, Ferguson TB, Cox JL.

Effect of neurotransmitters on the activation sequence of the isolated atrium.
Schuessler RB, Bromberg BI, Boineau JP.

Left ventricular pressure effects on right ventricular pressure and volume outflow.
Damiano RJ Jr, Cox JL, Lowe JE, Santamore WP.

Computerized potential distribution mapping: a new intraoperative mapping technique for ventricular tachycardia surgery.
Harada A, Tweddell JS, Schuessler RB, Branham BH, Boineau JP, Cox JL.

Effect of the right ventricular isolation procedure on ventricular vulnerability to fibrillation.
Damiano RJ Jr, Asano T, Smith PK, Cox JL.

Biatrial isolation--a new surgical treatment for supraventricular tachycardia.
Harada A, D'Agostino HJ Jr, Schuessler RB, Boineau JP, Cox JL.

Interpolating unipolar epicardial potentials from electrodes separated by increasing distances.
Blanchard SM, Damiano RJ Jr, Smith WM, Ideker RE, Lowe JE.

Pericardiocentesis guided by a pulse generator.
Tweddell JS, Zimmerman AN, Stone CM, Rokkas CK, Schuessler RB, Boineau JP, Cox JL.

Potential mapping in septal tachycardia. Evaluation of a new intraoperative mapping technique.
Tweddell JS, Branham BH, Harada A, Stone CM, Rokkas CK, Schuessler RB, Boineau JP, Cox JL.
Harada A, D'Agostino HJ Jr, Schuessler RB, Boineau JP, Cox JL.

Right ventricular free wall isolation: effects on regional myocardial blood flow.
Damiano RJ Jr, Asano T, Smith PK, Ferguson TB Jr, Cox JL.

Hemodynamic consequences of right ventricular isolation: the contribution of the right ventricular free wall to cardiac performance.
Damiano RJ Jr, Asano T, Smith PK, Ferguson TB, Cox JL.

Baroreflex modulation of heart rate and initiation of atrial activation in dogs.
Schuessler RB, Canavan TE, Boineau JP, Cox JL.

Effects of distant potentials on unipolar electrograms in an animal model utilizing the right ventricular isolation procedure.
Damiano RJ Jr, Blanchard SM, Asano T, Cox JL, Lowe JE.

Right atrial isolation: a new surgical treatment for supraventricular tachycardia. I. Surgical technique and electrophysiologic effects.
Harada A, D'Agostino HJ Jr, Schuessler RB, Boineau JP, Cox JL.

The effects of distant cardiac electrical events on local activation in unipolar epicardial electrograms.
Blanchard SM, Damiano RJ Jr, Asano T, Smith WM, Ideker RE, Lowe JE.

Left ventricular dysfunction and dilatation resulting from chronic supraventricular tachycardia.
Damiano RJ Jr, Tripp HF Jr, Asano T, Small KW, Jones RH, Lowe JE.

Electrophysiologic effects of surgical isolation of the right ventricle.

The electrophysiological effects of calcium channel blockade during standard hyperkalemic hypothermic cardioplegic arrest.
Ferguson TB Jr, Damiano RJ, Smith PK, Buhrman WC, Cox JL.

Effect of canine cardiac nerves on heart rate, rhythm, and pacemaker location.
Schuessler RB, Boineau JP, Wylds AC, Hill DA, Miller CB, Roeske WR.
Activation sequence and potential distribution maps demonstrating multicentric atrial impulse origin in dogs.
Boineau JP, Miller CB, Schuessler RB, Roeske WR, Autry LJ, Wylds AC, Hill DA.

Quantitative relation between sites of atrial impulse origin and cycle length.
Boineau JP, Schuessler RB, Roeske WR, Autry LJ, Miller CB, Wylds AC.

Microcomputer control of canine heart rate through chronotropic drug infusion.
Singh MC, Moyle DD, Singh G, Schuessler RB.

Widespread distribution and rate differentiation of the atrial pacemaker complex.
Boineau JP, Schuessler RB, Hackel DB, Miller CB, Brockus CW, Wylds AC.

Natural and evoked atrial flutter due to circus movement in dogs. Role of abnormal atrial pathways, slow conduction, nonuniform refractory period distribution and premature beats.
Boineau JP, Schuessler RB, Mooney CR, Miller CB, Wylds AC, Hudson RD, Borremans JM, Brockus CW.

Multicentric origin of the atrial depolarization wave: the pacemaker complex. Relation to dynamics of atrial conduction, P-wave changes and heart rate control.
Boineau JP, Schuessler RB, Mooney CR, Wylds AC, Miller CB, Hudson RD, Borremans JM, Brockus CW.
Protocol Title: Neuropharmacology of Pontine Control of Breathing Frequency
VA Station: Milwaukee

Status of research with dogs: approved, no further work with dogs is anticipated on this protocol as principal investigator has retired from VA, so work on this protocol is technically “inactive”, but it is included here because the IACUC approval has not yet expired, and additional work with dogs could still be done if the ongoing analysis of the data collected from this protocol, and reviewer comments, require it.

The publications listed below were the result of work by Dr. EJ Zuperku and his colleagues. Most of the research is very basic in nature—characterizing mechanisms underlying the central control of breathing. The most recent studies involved the neurophysiology/pharmacology of the effects of volatile anesthetics and mu-opioids in producing respiratory depression. The studies in dogs made it possible to pin-point the anatomical region in the pons, where respiratory-related neurons are strongly depressed by clinically relevant concentrations of mu-opioids and cause severe slowing of breathing rate and complete arrest. Microinjection of naloxone into this small region reversed the respiratory rate depression. The reduction in tidal volume induced by opioids appears to occur by depression of neurons in the medulla. An understanding of the neurotransmitter/modulator properties of these opioid sensitive neurons will contribute to the development of therapeutic measures to counteract opioid-induced respiratory depression. (Citations are listed with the earliest publications first.)


Protocol Title: Autonomic Nerve Activity and Cardiac Arrhythmias
VA Station: Richmond
Status of research with dogs: approved, work with dogs is ongoing

(Citations are listed with the most recent publications first.)


Protocol Title: Effect of Chronic Premature Ventricular Contractions on the Remodeled Ischemic Heart
VA Station: Richmond
Status of research with dogs: approved, work with dogs is ongoing

(Citations are listed with the most recent publications first.)


Protocol Title: Nanoparticle Injection into Ganglionated Neural Plexi to Prevent Atrial Fibrillation
VA Station: Richmond
Status of research with dogs: approved, work with dogs is ongoing

(Citations are listed with the most recent publications first.)


Protocol Title: A Comparison of Canine Anesthetic Regimens to Optimize Hemodynamic Stability and Quality of Electrophysiologic and Neurophysiologic Data Acquisition
VA Station: Richmond
Status of research with dogs: approved, work with dogs is ongoing

This protocol is designed to clarify how the various anesthetic regimens in use for dogs impact the hemodynamics, electrophysiology, and neurophysiology that are under study in protocols such as the other three IACUC-approved protocols being conducted in Richmond. Therefore, all of the publications listed for those three protocols are also relevant to this one. In addition, the published literature regarding the development of these anesthetic regimens, and understanding how they work and how they impact physiological systems, is also associated with this work.