RatCVS - Rat Cardiovascular System Simulation

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Introduction

RatCVS is a simulation of a pithed rat experimental preparation for investigating the actions of drugs on the cardiovascular system. The 'pithed rat' experimental model was developed by R.E. Shipley in the late 1940s to investigate the action of drugs on blood pressure and heart rate. It was used extensively in the subsequent decades to characterize the action of drugs acting on the cardiovascular system and the types of receptors mediating the responses to drugs and remains in use to some extent to this day.

"Pithing" refers to the destruction of spinal cord pathways by the insertion of a metal rod into the spinal column, severing all the nerve connections between the brain and the cardiovascular system. In a normal rat, the central baroreceptor reflex system greatly complicates the interpretation of observed changes in blood pressure and heart rate caused by the administration of a drug. Any drug-induced increase in blood pressure causes a reflex slowing of the heart rate making it difficult to separate the direct drug effect from the indirect reflex. By removing these central baroreceptor reflexes, pithing makes the study of drug effects much easier. In addition, the pithing wire in the spinal columm allows the selective electrical stimulation of sympathetic nerve pathways to the heart and vasculature.

This simulation allows you to observe traces of **blood pressure, left ventricular pressure, venous pressure, heart rate** and **contractile force** on a simulated chart recorder, to apply a variety of different drugs, and to observe their effects

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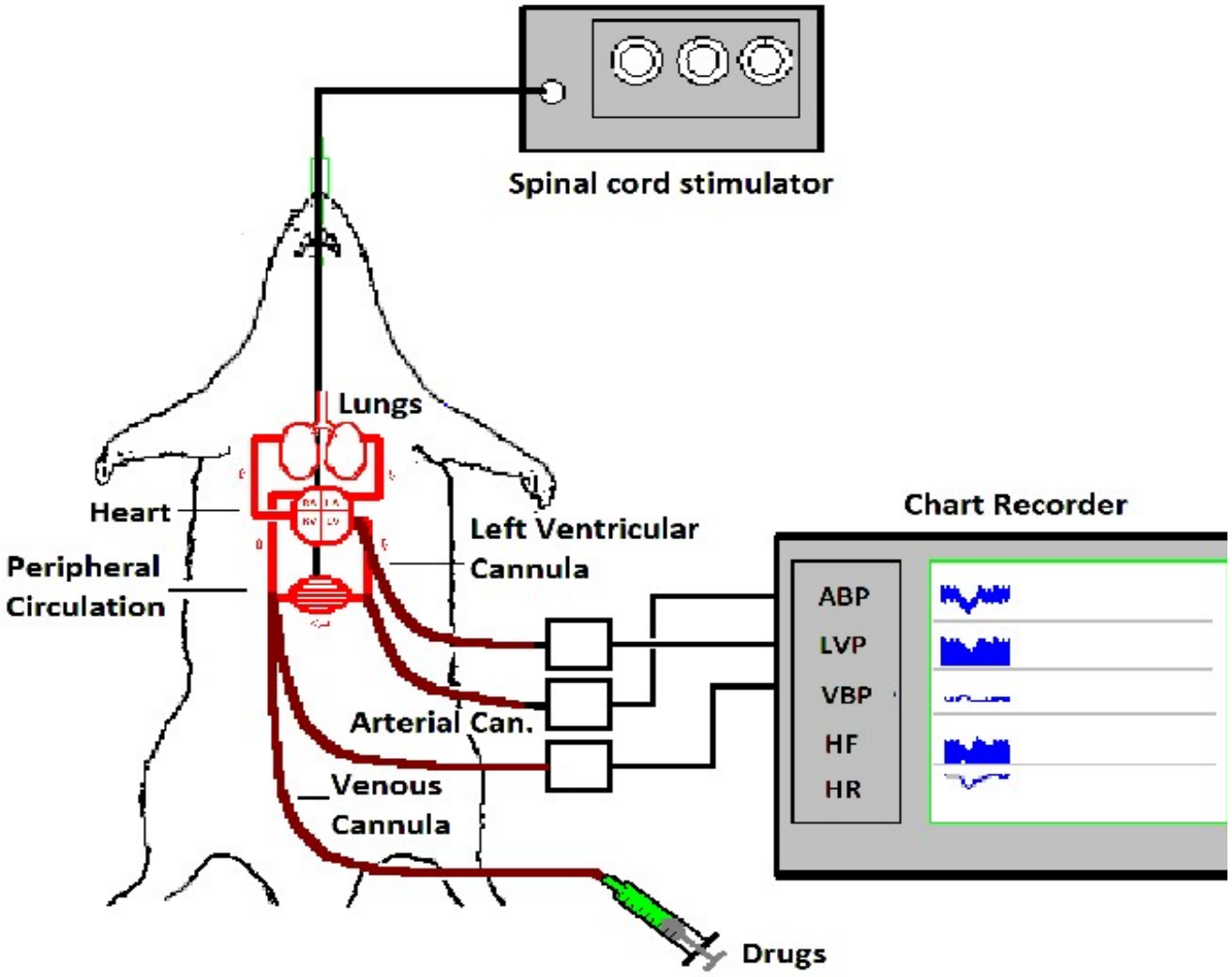
Rat Cardiovascular System Preparation



A rat is anaesthetised and artificially ventilated. Three cannulae are inserted into the femoral artery, vein and the left ventricle of the heart. A specially designed pithing rod is passed down the spinal cord of the animal destroying all nerve connections with the brain, and hence disabling the central blood pressure reflexes associated with the carotid artery baroreceptors.

ABP: The **arterial cannula** is connected to a pressure transducer to measure arterial blood pressure. Traces of arterial blood pressure (ABP mmHg) are recorded on the chart recorder.

LVP: The **left ventricular cannula** is connected to a second pressure transducer and used to produce a trace of left ventricular pressure (LVP mmHg).

VBP: The **venous cannula** is connected to a third pressure transducer and used to produce a trace of central venous blood pressure (VBP mmHg). Drugs can also be injected into the animal via the venous cannula.

HF: The **heart force** is a measure of heart contractile force.

HR: The **heart rate** is calculated from the ABP trace and shows number of heart beats per minute.

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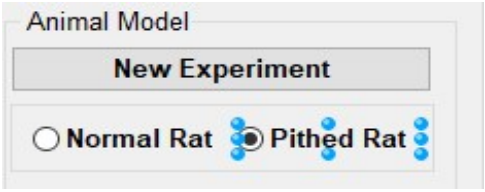
Using the Simulation

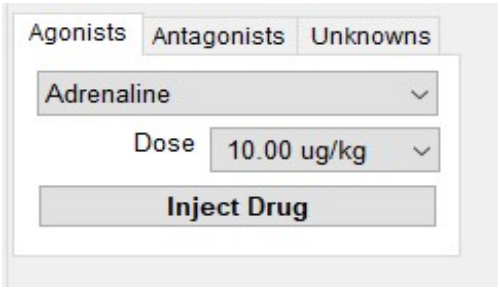
1) Select the experimental model you want to use: **Pithed Rat** for a pithed rat experiment (where a pithing wire has been inserted into the spinal cord) or **Normal Rat** for an experiment on a rat with an intact spinal cord and full baroreceptor reflexes.



Then click **New Experiment** to initiate the experiment. (Note. Clicking **New Experiment** will clear any existing experimental results from the chart.).

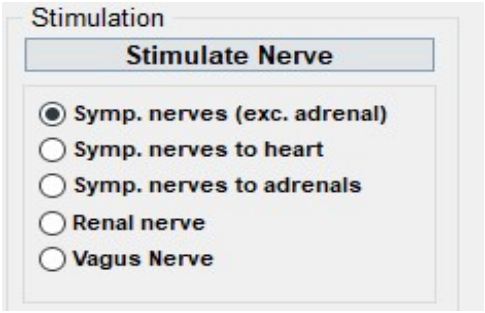
2) Click the **Start** button to start the chart recorder running.

3) To inject a drug into the animal's circulation : select a drug from from either the **Agonist** or **Antagonist** list or an unknown drug from the **Unknowns** list.



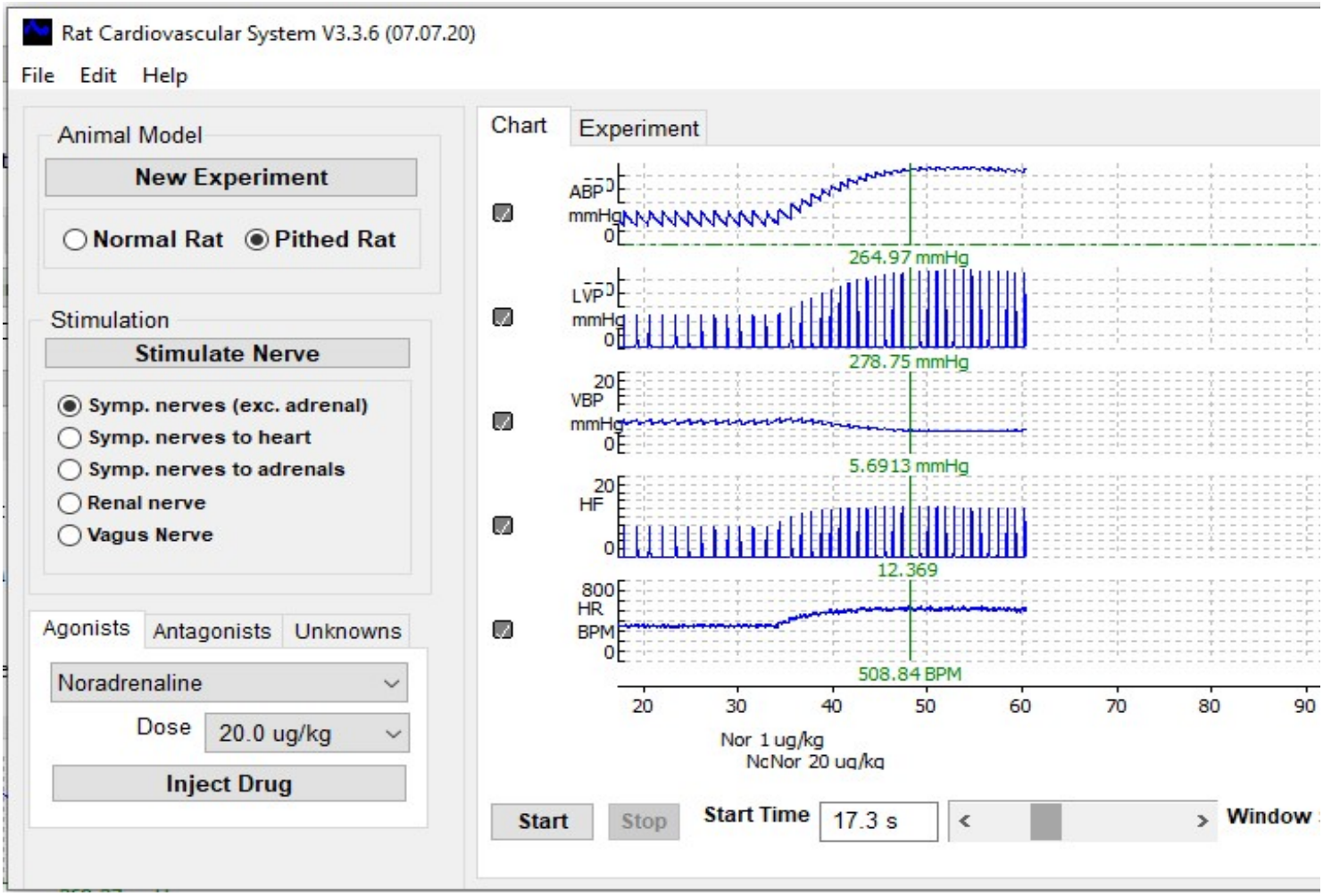
Then select the dose to be injected and click the **Inject Drug** button. The name and dose of drug injected is indicated on the chart trace.

4) To observe the effect of electrically stimulating various nerve pathways, select the nerve pathway and click the **Stimulate Nerve** button.



The stimulated nerve is indicated on the chart.

5) You can add as many doses and/or different drugs and/or nerve stimuli as necessary. When you have finished your experiment, click the **Stop** button to stop the chart.



6) You can scroll backwards and forwards through the recording using the slider bar below the chart and/or change the duration of the display window by entering a new value into the **Window Size** box or by clicking the arrow buttons on either side.

7) To make quantitative measurements from the traces, drag the green vertical readout cursor over the trace and note the numerical values of the traces on the display.

8 To copy a picture of the chart recording to the Windows clipboard for pasting into a report, select **Copy Image** from the **Edit** menu.

9) To print out a hard copy of the chart recording , select **Print** from the **File** menu.

10) When you have completed an experiment you can save it to a storage file by selecting **Save Experiment ...** from the **File** menu. (To re-load an experiment, select **Load Experiment ...**).

11) To exit from the simulation program, select **Exit** from the **File** menu.

Receptors

Receptor types and drug targets present on heart and blood vessel and action on tissues.

Tissue	Receptor / target	Action
Heart	β1-adrenoceptor	Increases heart rate and force
"	Muscarinic cholinoceptor	Decreases heart rate and force
"	Adenosine	Decreases heart rate and force
"	Calcium ion channels	Blocking Ca channels decreases heart rate and force
"	Sodium/Potassium pump	Blocking Na/K pump increases heart force
Blood vessels	α1-adrenoceptor	Vasoconstriction
"	β2-adrenoceptor	Vasodilation
"	Potassium ion channels	Opening of K channels causes vasodilation
"	Nitric Oxide	Vasodilation
"	Angiotension converting enzyme	Inhibition of ACE causes vasodilation
"	Angiotension II receptor	Vascostrictrion

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Drugs

Drugs and their receptors.

Drug	Receptor
Adrenaline	$\alpha+\beta$-adrenoceptor agonist ($\alpha+\beta$ potency)
Noradrenaline	$\alpha+\beta$-adrenoceptor agonist ($\alpha>\beta$ potency)
Isoprenaline	$\alpha+\beta$-adrenoceptor agonist ($\alpha<\beta$ potency)
Phenylephrine	α-adrenoceptor agonist
Acetylcholine	Cholinoceptor agonist
Glyceryl Trinitrate	Nitric oxide
Cromakalim	Potassium channel opener
Angiotensin II	Angiotensin II receptor agonist
Digoxin	Sodium/Potassium pump inhibitor
Milrinone	Phosphodiesterase inhibitor
Adenosine	Adenosine receptor agonist
Propanalol	β-adrenoceptor antagonist
Atenalol	$\beta 1$-adrenoceptor antagonist
Atropine	Muscarinic cholinoceptor antagonist
Phentolamine	α-adrenoceptor antagonist
Prazozin	$\alpha 1$-adrenoceptor antagonist
L-NOARG	Nitric oxide synthase inhibitor
8-SPT (8-parasulphophenyltheophylline)	Adenosine receptor antagonist
Captopril	Angiotensin converting enzyme inhibitor
Verapamil	Calcium channel blocker.
Losartan	Angiotension II receptor antagonist
Glibenclamide	Potassium channel blocker

Acknowledgements

This simulation was developed in the Dept. of Physiology and Pharmacology at the University of Strathclyde, starting in 1996. Thanks are due to Profs. Brian Furman, Kathy Kane, Cherry Wainwright and Roger Wadsworth, the cardiovascular pharmacology group at that time, who conceived the need for the simulation as a teaching aid, specified its aims and objectives, and selected the drugs and receptor systems to be covered.

It is worth also remembering the original developer of the method, R.E. Shipley (1947) and those who extended it such as Gillespie et al. (1970) and others from the Physiology and Pharmacology departments at the University of Glasgow (Bulloch et al., 1987).

Shipley R.E. & Tilden J.H. (1947) Pithed Rat Preparation Suitable for Assaying Pressor Substances. Proc. Society for Experimental Biology and Medicine, 64 453-455.

J S Gillespie J.S., Maclaren A, Pollock D. (1970) A method of stimulating different segments of the autonomic outflow from the spinal column to various organs in the pithed cat and rat. Br J Pharmacol. 40(2):257-67.

Bulloch JM, Docherty, JR Flavahan NA , McGrath JC & McKean CE (1987) Difference in the potency of a2-adrenoceptor agonists and antagonists between the pithed rabbit and rat. Br J Pharmacol. 91(3) :457-66.