Journal of Pharmacological and Toxicological Methods 81 (2016) 99–106

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Unlock the information in your data: Software to find, classify, and report on data patterns and arrhythmias

Anil C. Mehendale *, Jennifer M. Doyle *, Christopher M. Kolin, John P. Kroehle Jr.

Data Sciences International, 119 14th St NW, Suite 100, St. Paul, MN 55112, United States

ARTICLE INFO

Article history:
Received 1 March 2016
Received in revised form 9 May 2016
Accepted 12 May 2016
Available online 16 May 2016

Keywords:
Arrhythmia
Automated analysis
Cardiovascular safety
ECG
Jacketed Telemetry
Methods
Nonclinical
Pattern recognition
Telemetry
Toxicology

ABSTRACT

Introduction: Safety studies generate a significant volume of waveform and calculated data. The verification of calculated data and the process of searching through these data for patterns of interest (including arrhythmias) is time intensive. Data Insights™ has been developed for the Ponemah™ software platform to provide efficient verification and search capabilities.
Methods: Searches may be constructed using calculated and pattern matching data available in Ponemah. Searches are composed of one or more search clauses that may be combined using Boolean operators (AND, OR). Each search clause is a Boolean expression composed of inputs and functions. Data Insights includes a number of predefined species-specific searches for arrhythmias that were qualified for canine, non-human primate and minipigs. Qualification compared arrhythmias identified using Data Insights against a board-certified veterinary cardiologist hand-scored reference datasets.
Results: In seven out of eight arrhythmia types, arrhythmia incidences identified by Data Insights were congruent to those identified by hand-scoring. Premature Atrial Contractions (PACs) accounted for the only discrepancy in hand scored data-segments, although all overt PACs identified by the veterinary cardiologist were also identified by Data Insights. Unscored atrio-ventricular blocks accounted for the remaining differences.
Discussion: Data Insights may be used to support different applications, as searches may be created for any physiologic signal type. Its interactive dialog permits rapid review of search results and a dynamic method for handling outliers, signal noise, and false positives. Data Insights provides an efficient method to locate, present, and report on data patterns and anomalies for accurate, consistent results.

1. Introduction

Over the past few decades, improvements to data acquisition and analysis systems have led to an increase in the volume of physiological data collected for drug development and the level to which these data are being analyzed has increased dramatically. The amount of data for a typical continuous 24-h acquisition in a safety pharmacology study could be on the order of 100,000 cardiac cycles, or more, per animal. The desire to combine safety pharmacology endpoints in toxicology studies increases the number of such acquisitions (Pettit, Berridge, & Sarazan, 2010). Analyzing large datasets adds another burden on the researcher performing the analysis, increasing the analysis time and operational cost while demands for time and financial efficiencies are equally high. Semi-automated analysis methods are available; however, thoroughly auditing analysis results is also time consuming.

The presence of unexpected arrhythmias have been associated with the withdrawal, or restricted use, of many pharmaceuticals (Piccini et al., 2009). Current methods for arrhythmia analysis typically rely on hand-scored or semi-automated analysis on a representative sample consisting of only a few cardiac cycles at selected time point(s) throughout the ECG data and do not provide an efficient or comprehensive detection method.

In response to these needs, Data Sciences International (DSI) developed Data Insights™ for the Ponemah™ software platform. Data Insights allows the researcher to assess the quality of their data analysis and target problem areas for additional cleaning and analysis without having to manually over read the dataset. Data Insights reveals these

Abbreviations: ar_V Ectopic, the "ar_" prefix indicates default Data Insight arrhythmia searches (For example, ar_V ectopic refers to an arrhythmia search for ventricular ectopic cycles); Cyc, cycle is used by Data Insights to identify cycles relative to the current cycle (cyc0); ECG, electrocardiogram; HR, heart rate in beats-per-minute computed by Ponemah as the reciprocal of the RR-I (in seconds) for the cardiac cycle multiplied by 60; JET, Jacketed External Telemetry; LVEDP, left ventricular end diastolic pressure; Num, a sequential number Ponemah assigns to each cardiac/respiratory cycle; PAC, Premature Atrial Contraction; PCt, P wave count representing the number of valid P waves marked by the Ponemah ECG analysis module within a user-defined logging period; PR-I, PR interval is the time interval (in milliseconds) between the beginning of atrial depolarization and the beginning of ventricle depolarization; PVC, Premature Ventricular Complex; QRS width, QRS width is the time interval (in milliseconds) of the QRS complex from the Q wave to the S wave; RR-I, RR interval is the time interval (in milliseconds) from one R wave to the previous R wave; SSD, Solid State Drive; Sys, systolic blood pressure.

* Corresponding authors.

http://dx.doi.org/10.1016/j.vascn.2016.05.007
1056-8719/

problem areas by applying user-defined search rules to the dataset and displaying cycles that match the search criteria. Match results are displayed in graphical and tabular formats to provide researchers a multi-faceted view of each search result and how the results are distributed throughout their dataset. This provides researchers the necessary information to better understand their data and make an informed decision on whether or not to exclude certain sections of data due to signal artifact or data dropout without investing a significant amount of time.

In addition to searches for data validation and analysis, researchers may create Data Insights searches to locate, present, and report on any data pattern or anomaly within the dataset, e.g., cardiac arrhythmias. The use of Data Insights permits the user to move beyond snapshots of data for efficient coverage of large volumes of data.

Using Data Insights searches, researchers can optimize their data review and analysis process to achieve consistent, reproducible results for reporting purposes.

2. Methods

In this section we present the salient features included in Data Insights to permit the design and editing of search definitions and interactive processing of results, Data Insights application to arrhythmia detection, and the steps taken to qualify Data Insights functionality and usability.

2.1. Search definition

Searches are composed of one or more search clauses that may be combined using Boolean operators (AND, OR). Each search clause is a Boolean expression composed of inputs and functions. The inputs include amplitude and timing data calculated by Ponemah (RR interval, heart rate, LVEDP, etc.), pattern matching results, and time of day information. The functions determine how inputs are used when evaluating the Boolean expression that forms a search clause. A few examples are provided in Table 1. Existing search definitions may be modified or new search definitions may be created by the user. One or more search definitions may be associated with each acquired signal. The relationship between raw signals, derived cycle information, and Data Insights is shown in Fig. 1.

2.2. Result processing and threshold determination

The following features assist in the processing of large sets of results and the identification of appropriate thresholds for use in search definitions.

2.2.1. Display of search inputs

Each search input used in a search definition is represented in the Results Derived View as shown in Fig. 2. Each search result is represented by a row in the Results Derived View which displays the values for each search input, providing an understanding of why a search result met the search criteria.

2.2.2. Visualization of results

Each search result is displayed in the Results Wave View separated by a dashed green line. The range of time displayed for each result depends on the range of data that contributes to the result.

Results are also displayed in a histogram as shown in Fig. 3. The width of each histogram bar corresponds to a user defined bin length, which only impacts the visualization of the data. The height of each green histogram bar corresponds to the number of matches in the bin. The red regions indicate the location and number of matches that are currently displayed in the Results Wave View.

If the usable data in a bin drops below the value specified in the Data Percentage field, the background of the bin will change to a coral color (not shown). This alerts the user to regions that have a break in acquired data or have lost a significant amount of data to noise.

2.2.3. Sorting by search input

By default, the search results are ordered by time although the search results may be sorted by any of the columns in the Results Derived View. Sorting updates the order of results in both the Results Derived View and the Results Wave View. In Fig. 2, results are sorted by the %Decrease column.

2.2.4. Bulk handling of results

Multiple results may be selected and either rejected as not belonging to the set of results or marked as bad data to prevent further analysis on the data samples.

2.2.5. Synchronization with graph pages

Each result may be synchronized with standard graph pages and derived listings to provide additional context to the result.

2.3. Arrhythmia detection: Searches

Data Insights includes a number of predefined species-specific searches; canine defaults are listed in Table 2. The default searches are suitable for most subjects. If required, a subject's search may be modified to account for variation specific to the subject. A sample workflow for identifying arrhythmias is also shown in Fig. 4. Clauses related to search result duration and noise sensitivity are not shown.

2.3.1. Ventricular ectopic derivatives

Searches for Premature Ventricular Complexes (PVCs), escape beats, interpolated beats, ventricular bigeminy, trigeminy, couplets, triplets and runs are available as extensions to cycles identified as ventricular ectopics. PVCs, escape beats and interpolated beats are identified by examining the inter-beat intervals preceding and following the ventricular beat. Ventricular couplets, triplets and runs are identified using Series

Table 1
Example Data Insights' search definitions and corresponding cycle identification description illustrating the diversity of searches that can be created using any acquired signal's (ECG, left ventricular pressure, systemic blood pressure, etc.) derived data and ECG waveform morphology using ECG Pattern Recognition Option (PRO).

Search definition	Cycle identification
Value(Sys_{cyc0}) > 170	Identifies all cycles where the systolic value is greater than 170 mmHg.
%Decrease($RR\text{-}I_{cyc\text{-}1}$, $RR\text{-}I_{cyc0}$) > 30	Identifies all cycles that show a decrease in the RR interval of more than 30% from the previous cycle (cyc-1) to the current (cyc0). Functions that are similar to %Decrease() are %Increase(), %Change(), Increase(), Decrease() and Change().
Template(ECG_{cyc0}) = Ventricular Ectopic	Identifies all cycles that match templates tagged with a ventricular ectopic tag.
Search($_{cyc0}$)!= ar_PAC	Identifies all cycles that do not match a PAC search. A Search() function would typically be used in conjunction with other clauses.
RealTime() > 08:00:00 AND RealTime() < 20:00:00	Identifies all cycles that fall between 8:00 AM and 8:00 PM within each 24 h cycle, such a search would typically be used in conjunction with other clauses.
Series(ar_V Ectopic, 1)=2	Identifies multiple occurrences of a pattern. In this example, all instances where exactly two consecutive cycles match an ar_V Ectopic search are identified.

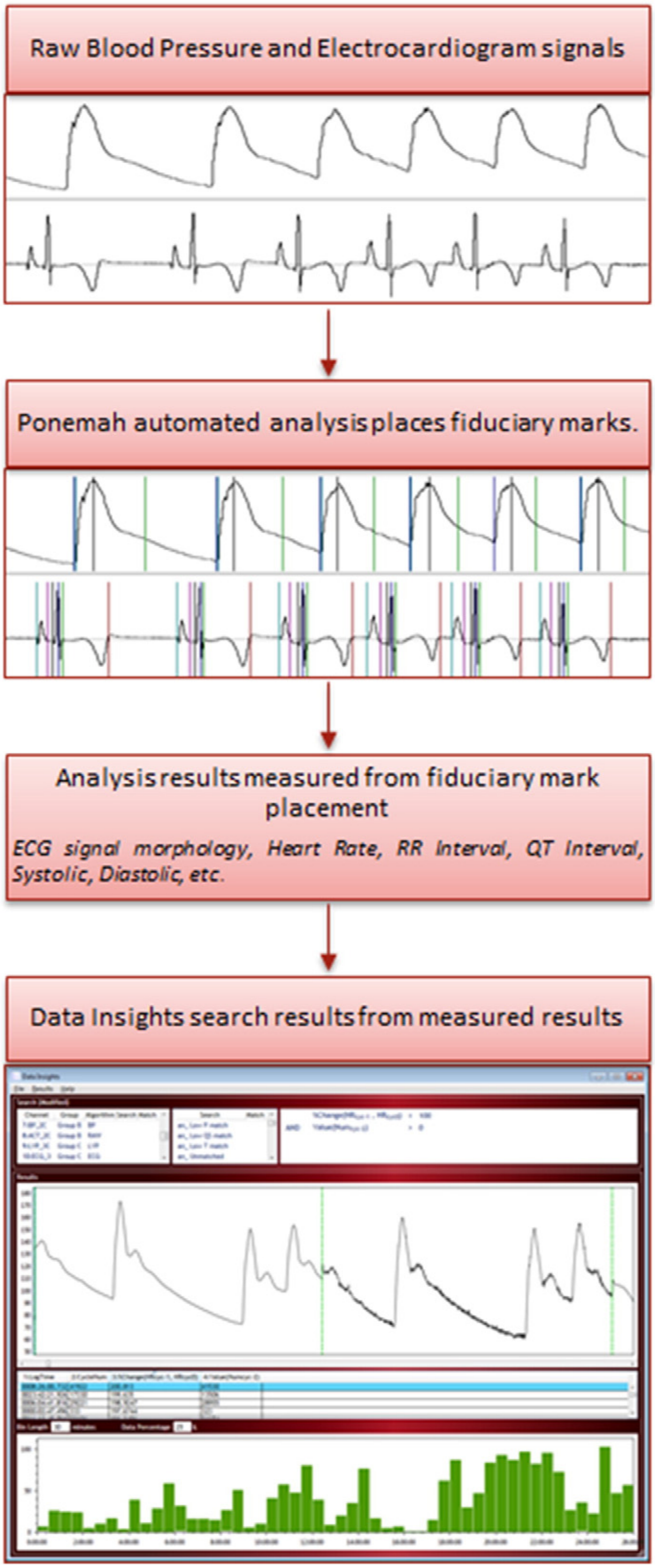


Fig. 1. Relationship between raw signals and derived parameters for searches used in Data Insights. RAW signals are analyzed using Ponemah's automated analysis modules to place the fiduciary marks. From the mark placement, analysis results are calculated to report derived measurements. These measurements are then used within Data Insights' search definitions to locate, present, and report data patterns and anomalies.

based searches that look for contiguous ventricular ectopics. Ventricular bigeminy and trigeminy are also identified using Series based searches that look for repeating ventricular ectopics that are separated by sinus beats.

2.4. Arrhythmia detection: Process

An outline of the process used to identify arrhythmias with Data Insights is shown in Fig. 4.

2.5. Internal qualification

The species-specific default arrhythmia search definitions available in Data Insights were qualified for canine, non-human primate, and minipig by comparing arrhythmias identified using Data Insights against hand-scored reference data-segments. Hand-scoring was performed by a board-certified veterinary cardiologist on 41 data-segments. Each data-segment was 15 min in duration, for a cumulative total of 10.25 h of data.

The data-segments were analyzed independently by the cardiologist and a Data Insights operator. Analysts were blinded to the results until each dataset was fully analyzed by the respective method.

Tables 3 and 4 detail the species and acquisition methods for the data-segments. These data-segments were selected based on the known existence of at least one arrhythmia.

2.6. External qualification

Data Insights was provided to two Beta sites for evaluation within their environment.

At Charles River Laboratories (Reno, NV), a previously conducted ascending-dose study that had triggered an extensive over read by a veterinary cardiologist was evaluated using Data Insights. Data Insights results were compared with the existing qualitative arrhythmia report from the veterinary cardiologist.

The study data consisted of 12 datasets with at least 26 h of data from 3 canines (prestudy and 3 ascending doses). The cardiologist examined 13, 15-min segments per 26 h recording and provided a qualitative assessment of the arrhythmias found. Over read results were available every hour from 2 h predose to 6 h postdose and at 8, 12, 18 and 24 h postdose.

The Data Insights analyses were not limited to the snapshots examined by the cardiologist and were conducted on all available data. The process used to analyze the data is outlined in Fig. 4.

In a separate study, a biopharmaceutical company ran a repeat dose toxicology study for a potential drug candidate, requiring a detailed analysis to identify ventricular arrhythmias over a 20-h data acquisition period in 40 Jacketed External Telemetry (JET) instrumented non-human primates at prestudy, weeks three and five of dosing, and week eight of recovery, for a total of 3200 h of data. The biopharmaceutical Company used Ponemah with and without the use of Data Insights for the identification of arrhythmias for the prestudy day. The investigators deployed Data Insights to automate their arrhythmia assessment for the subsequent study days (total of 3200 h of data). The study compared results and analysis time of each method.

3. Results

3.1. Internal qualification

A total of 1615 second degree atrio-ventricular blocks were observed in 3/41 data segments, with the remaining 38/41 data segments only showing a total of 12 second degree atrio-ventricular blocks. The three data-segments that contained a large number of atrio-ventricular blocks were not hand scored in their entirety and are reported separately.

Table 5 compares the results of arrhythmias identified by Data Insights and hand-scoring from 38 data segments. In seven out of eight arrhythmia types, arrhythmia incidences identified by Data Insights were congruent to those identified by hand-scoring. Premature Atrial Contractions (PACs) accounted for the only discrepancy. Detecting PACs can be complicated by naturally varying P-P intervals which confound

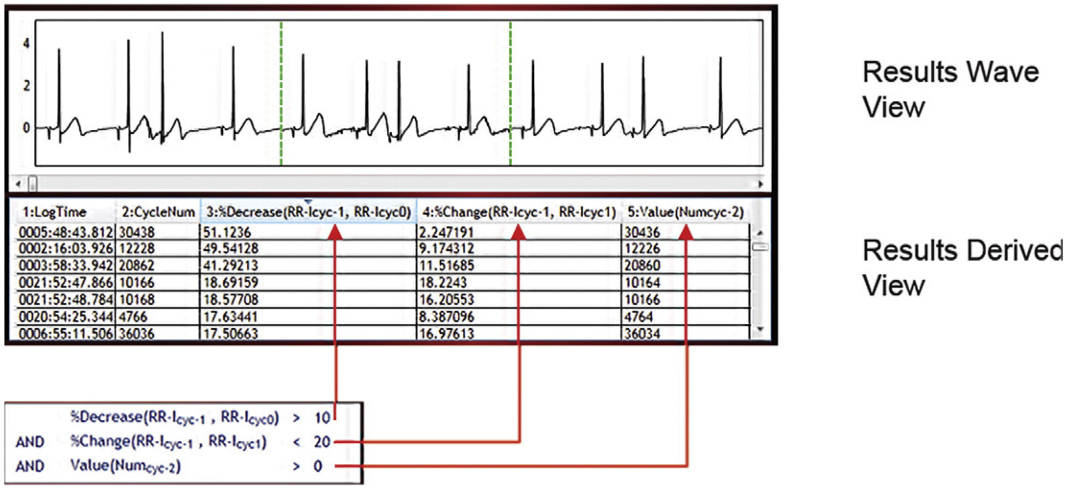


Fig. 2. User interface of Data Insights displaying the Results Wave View and Results Derived View, as well as the relationship between Derived View columns and search inputs. The results listed in the Derived View correspond to those displayed in the Wave View. Each column in the Derived View contains the calculated data for each search definition clause, allowing the user to understand why the result is a match. User may sort on the column headers to organize the results displayed in the Wave View to easily browse through results.

the definition of prematurity. In some cases a designation relies largely on judgment, not simply measurements. The three instances noted by the veterinary cardiologist that were not identified by Data Insights were labeled by him as “possible PACs”. All overt PACs identified by the veterinary cardiologist were also identified by Data Insights.

The remaining three data-segments were evaluated in two steps, first by reviewing matches for false positives and next Data Insights was used to view the differences between a more inclusive search and the results of the atrio-ventricular block search; thus identifying instances of atrio-ventricular blocks that were initially missed. Out of 1615 second degree atrio-ventricular blocks, 1514 were correctly identified with 12 false positives and 101 false negatives. The incorrectly identified beats occurred when a P wave was too close to the preceding T wave.

False positives were also encountered with PAC and Junctional searches. A total of 944 false positive PACs were found. False positives are expected in the case of PAC searches, especially in the presence of sinus arrhythmia. Adjudication of PAC results is greatly simplified by sorting based on the decrease in RR interval. Sorting in this fashion permits the reviewer to view the highest value results first and once normal beats are encountered it facilitates rejecting the remaining results. Twenty-three false positive Junctional Beats were found, due to the presence of small P waves were not marked.

3.2. External qualification

At Charles River Laboratories, analysis of the data from the 3 canines yielded low incidences of arrhythmias (PAC, PVC, 2nd degree atrio-ventricular block) were found in all prestudy, low dose and mid dose acquisitions, as well as in two of the three high dose acquisitions. This finding was consistent with the results reported in the veterinary cardiologist's qualitative report. The third high dose acquisition showed a rise in ventricular ectopy from 3 to 6 h post dose which was consistent with the results reported by the veterinary cardiologist.

The biopharmaceutical company found that Data Insights provided a more accurate, comprehensive arrhythmia assessment that was consistent with published literature and required less time than analysis without Data Insights. ECG analysis time, including arrhythmia analysis, was reduced by approximately 50% relative to the analysis without Data Insights. Analysis time was mainly driven by the amount of signal noise present in the JET data. Data Insights' tools were more efficient for managing signal noise and excluding these data as compared to standard signal noise rejection methods. Data Insights also identified ventricular arrhythmias in 16 of 40 subjects compared to only eight when using template based analysis over the same range of data. Among these eight subjects, Data Insights identified additional arrhythmias in four of the subjects. Data Insights provided an additional diagnostics component by further differentiating ventricular arrhythmias into variants such as bigeminy and trigeminy. During the 20-h prestudy day, analysis with Data Insights determined that 40% of the non-human primates had ventricular arrhythmias, compared to only 20% when not using Data Insights. The results obtained from Data Insights were in close agreement with the ventricular arrhythmia rates and incidences reported in the literature. (Chui, Derakhchan, & Vargas, 2012; Cools et al., 2011; Gauvin, Tilley, Smith, & Baird, 2006).

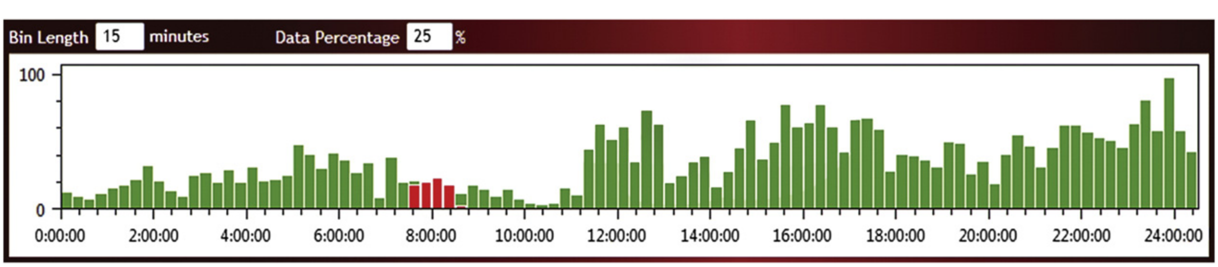
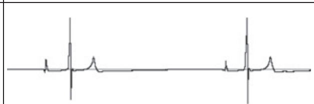
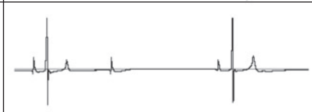
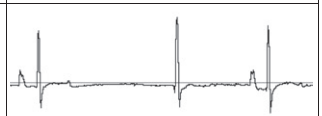
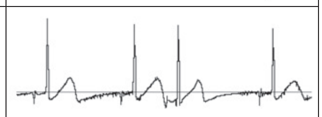
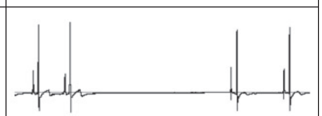
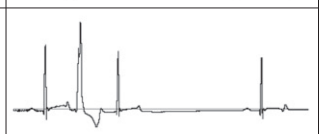
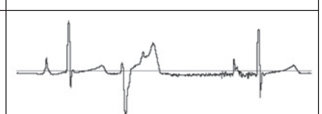
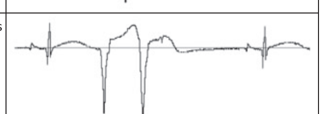
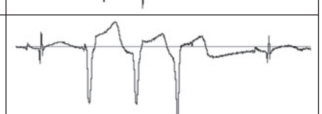
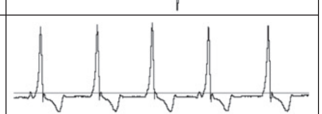
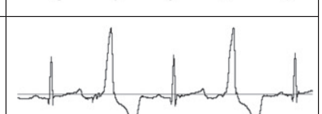
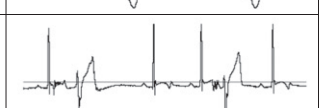


Fig. 3. Histogram displaying distribution of search results. The red colored bars indicate the currently displayed results in the Results Wave View, providing the user with context as to the location of these results within the dataset.

Table 2
Data Insights default arrhythmia search definitions for canines. Each definition includes a description of the search, the representative Boolean expression, and an example waveform morphology.

Search Definition	Waveform Morphology
First-degree AV block: Identifies cycles that have a long PR interval that is shorter than the PR interval for a potential isolated P wave Value(PR-I_{cyc0}) > 130 AND Value(PR-I_{cyc0}) < 250	
Second-degree AV block: Identifies cycles that have a significantly elongated PR intervals. This search is used after marking isolated P waves. Value(PR-I_{cyc0}) > 250	
Junctional Complex: Identifies cycles that do not have a P or have a P with a short PR interval and are not Ventricular Ectopics (Value(PCt$_{cyc0}$) = 0 OR %Decrease(PR-I_{avg0}, PR-I_{cyc0}) > 35) AND Search($_{cyc0}$) != ar_V Ectopic	
Premature Atrial Complexes: Identifies cycles that show a decrease in RR interval relative to the previous cycle, while showing little change in RR interval between the previous and following cycles. %Decrease(RR-I_{cyc-1}, RR-I_{cyc0}) > 30 AND %Change(RR-I_{cyc-1}, RR-I_{cyc1}) < 25	
Sinus Pause: Identifies cycles with a long RR interval or a marked increase in RR relative to the previous cycle. Value(RR-I_{cyc0}) > 3000 OR %Increase(RR-I_{cyc-1}, RR-I_{cyc0}) > 200	
Ventricular Interpolated: Identifies when a ventricular beat is inserted within normal sinus beats. %Decrease(RR-I_{cyc-1}, RR-I_{cyc0}) > 40 AND %Change(RR-I_{cyc0}, RR-I_{cyc1}) < 35 AND %Decrease(RR-I_{cyc2}, RR-I_{cyc1}) > 40 AND Search($_{cyc0}$) = ar_ V Ectopic Single	
Ventricular Ectopic: Identifies cycles with a widened QRS. Value(QRS$_{cyc0}$) > 54	
Couplet: Identifies two contiguous Ventricular Ectopic beats that are bracketed by two sinus (non-ventricular) beats. Series(ar_ V Ectopic, 1) = 2	
Triplet: Identifies three contiguous Ventricular Ectopic beats that are bracketed by two sinus (non-ventricular) beats. Series(ar_ V Ectopic, 1) = 3	
Run: Identifies greater than three contiguous Ventricular Ectopic beats that are bracketed by two sinus (non-ventricular) beats. Series(ar_ V Ectopic, 1) > 3	
Bigeminy: Identifies a repeating pattern of two or more Ventricular beats that are separated by one sinus (non-ventricular) beat. Series(ar_ V Ectopic Single, 2) >= 2	
Trigeminy: Identifies a repeating pattern of two or more Ventricular beats that are separated by two sinus (non-ventricular) beats. Series(ar_ V Ectopic Single, 3) >= 2	

4. Discussion

4.1. Search flexibility

Data Insights' ability to work with derived results from all channels associated with a subject (ECG, blood pressure, respiration, temperature, etc.) permits a wide variety of searches. A spontaneous pause search on respiratory data from a rat in a whole body plethysmography chamber is shown in Fig. 5. In addition, cross channel searches may be constructed, for example, one could search for a dip in blood pressure that coincides with a change in RR interval or a widening of the QRS width, or one could look for a series of beats that exhibit a lengthening/shortening or increase/decrease in a derived parameter. Such flexibility in search design offers the unique ability to interrogate data in many novel ways, including cross-parameter correlations that were previously difficult to detect.

4.2. Arrhythmia detection

The predefined arrhythmia searches were validated for canine, non-human primate and minipig. Searches for mouse and rat are also available, however these searches have not been independently verified by a cardiologist.

The default ventricular ectopic search only depends on QRS width. RR interval relationships are excluded from the search to permit the identification of premature, as well as escape beats. The presence or absence of P waves is not included in this search either because a) QRS width is generally a sufficient discriminator, and b) P wave marking, especially in the presence of noise, is less precise than marking of the QRS complex. If a dataset requires monitoring the presence and placement of P waves, the addition of a search clause to confirm the absence of a P wave or the presence of a P wave that is physiologically inappropriate and could not have contributed to the subsequent ventricular depolarization can be added. The Junctional Beat search may be used as an example. Some wide QRS complexes may not be ventricular ectopics, but may represent bundle branch blocks or other conduction abnormalities. Such findings are less common and may be dealt with by using a Template clause or checking for the presence of a P wave. The default QRS width used in a canine search is 45 ms, this overlaps with the normal QRS range for canines (Smith, Tilley, Oyama, & Sleeper, 2016). Sorting based on QRS values permits rapid confirmation of an appropriate threshold.

In the default Junctional Beat search, Data Insights looks for beats that are not ventricular ectopics and either do not have a P wave or have a P wave with a shortened PR interval. The definition of a shortened PR interval is based on the percent change between the averaged PR interval in the period that contains the current cycle and the PR interval of the current cycle. This provides a species-agnostic search; however, this clause can easily be replaced with a Value based clause that uses a species or subject specific limit for defining a shortened PR interval.

Due to the lack of well accepted criteria for defining a sinus pause (Miller, Lehmkuhl, Bonagura, & Beall, 1999; Nelson & Couto, 2008; Silverstein & Hopper, 2014), two clauses were included in the sinus pause search, one based on the RR interval and another based on change in the RR interval from the previous cycle. The use of both clauses provides a more inclusive search result, the search may be modified to use a single clause by deleting the unwanted clause.

The premature atrial beat search makes the assumption that the premature beat resets the sinus node resulting in a normal RR interval following the premature beat (Ettinger & Feldman, 2009). In the presence of sinus arrhythmia, this search may result in a number of false positives, due to the variations in RR intervals. Sorting based on the percent decrease in the RR interval can help with processing of results.

The PR limit in the default search for first degree atrio-ventricular block in canines is set at 130 ms which is at the high end of the normal canine PR interval (Smith et al., 2016).

A number of default arrhythmia searches include a noise clause which permits the exclusion of noisy data from the results. Noise levels that interfere with R detection would typically warrant exclusion of the affected cycles from all analyses; however, a lesser noise threshold may come into play when working with T or P waves.

Short duration ECG traces are often acquired from restrained animals (snapshots) when looking for arrhythmias (Gauvin, Gauvin, Tilley, Smith, & Baird, 2009). This is primarily due to the time and cost associated with a comprehensive arrhythmia analysis. The use of Data

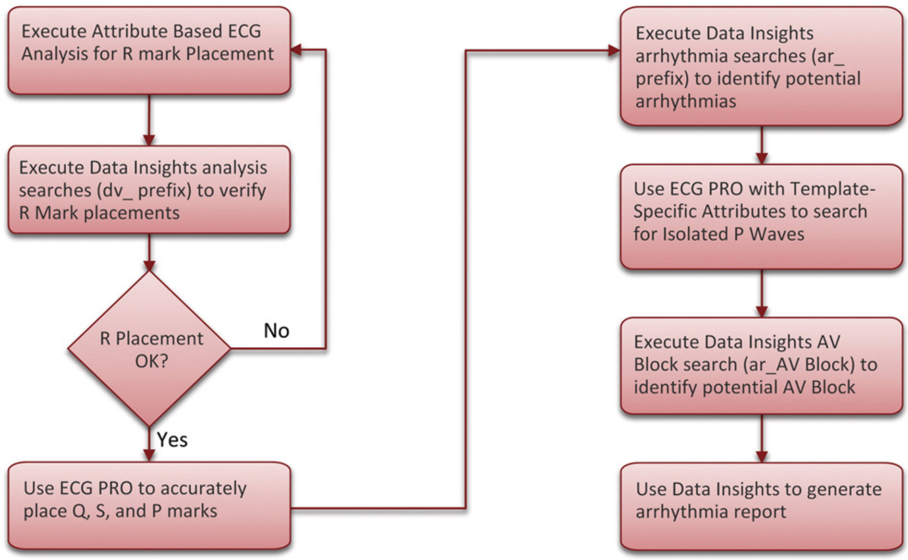


Fig. 4. Ponemah's ECG analysis and arrhythmia detection process as executed by the analyst for internal qualification. This is also the recommend process for users performing arrhythmia detection with Data Insights.

Insights makes it feasible to search for arrhythmias over entire datasets in freely moving animals, allowing a comparison of arrhythmia occurrence with the pharmacokinetics of the drug being administered in the absence of duress from physical restraint.

There is large inter- and intra-subject variability when looking at animal and human arrhythmias. This is why it is imperative to use a continuous 24-h collection period when looking at arrhythmias. The 24 h collection period is used due to the change of heart rates that occur during the light and dark cycle. Various arrhythmias are more prevalent at different heart rates, which occur at different times in the circadian rhythm (Cools et al., 2011).

In Authier 2010 publication, conflicting published results of the incident rate of premature ventricular beats using snapshot (10-s duration) review in restrained canines compared to continuous, freely moving canines. Review of 10 s of ECG data identified premature ventricular beats in 0.16% of the subjects, whereas reviewing continuous 18–24 h of ECG data identified premature ventricular beats in 19–26% of the subjects.

Table 3
Number of data-segments per species used for the internal qualification of Data Insights (n = 17).

Species	# Datasets
Canine	18
Non-human primate	17
Minipig	6
Total	41

Table 4
Number of data-segments used per acquisition method for the internal qualification of Data Insights (n = 17).

Acquisition method	# Datasets
Implantable Telemetry with solid tip lead	22
Implantable Telemetry with subcutaneous leads	4
Jacketed External Telemetry (JET) with surface leads	13
Epicardial leads	2
Total	41

Therefore, an arrhythmia review using 24 h of continuous data is recommended (Authier, Pugsley, Troncy, & Curtis, 2010; Cools et al., 2011; Curtis et al., 2013).

4.3. False positives

Setting search thresholds to permit a few false positives can increase confidence in the lack of false negatives. False positives can be rejected and false negatives may go unnoticed. Data Insights has been designed to simplify handling of false positives through visualization, sorting, and bulk processing of search results.

4.4. Handling outliers and noise

Signals acquired from freely moving test subjects often include noise artifacts, which may result in invalid marking of some cycles, and ultimately inaccurate derived output calculations. Today, commercial software platforms permit a certain level of data cleaning for basic data issues, such as telemetry dropout and motion artifact. Researchers will typically use graphical methods as an aid in determining areas of outlying data and then manually exclude these non-physiologic data from their results. Alternatively, researchers may use internally developed, custom tools (e.g. Excel macros or Matlab programs) to remove non-physiological data. Not only are these methods time consuming, they

Table 5
The comparison of the arrhythmia incidences found in the internal qualification dataset by the board certified cardiologist and those found independently by Data Insights (n = 17).

	Incidences found	
Arrhythmia type	Cardiologist	Data Insights
Ventricular ectopics	83	83
Junctional beats	38	38
Second degree atrio-ventricular block	12	12
Sinus pause	11	11
Premature Atrial Contraction	11	8
Ventricular bigeminy	8	8
Ventricular couplets	6	6
Interpolated beats	4	4

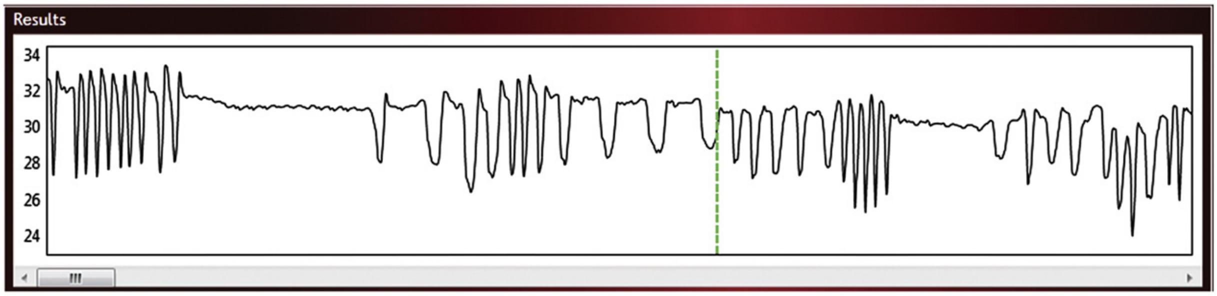


Fig. 5. Graphical results as displayed in the Data Insights Results Wave View from a spontaneous pause search executed on a respiratory signal obtained from a rat in a whole body plethysmograph chamber.

make study results difficult to reproduce by others who do not use the same methods.

Data Insights permits interrogation of beat by beat or averaged derived data. Incorrectly marked cycles or interesting data can often be isolated by searching on derived output parameters for extremes, or for large changes in consecutive values as shown below.

4.4.1. Heart rate limits search

This canine search for heart rate outliers, identifies all cycles that have heart rates above or below a normal range

$$\begin{array}{lll} & \text{Value}(\text{HR}_{cyc0}) & > \quad 250 \\ \text{OR} & \text{Value}(\text{HRcyc0}) & < \quad 30 \end{array}$$

4.4.2. Heart rate change search

This search for marked change in heart rate identifies all cycles that show an increase in RR interval (RR-I) of more than 50% from the current cycle to the next.

$$\%\text{Increase}(RR{-}\text{I}_{cyc0}, RR{-}\text{I}_{cyc1}) > \ 50$$

Use of an outlier search early in the analysis process is useful to confirm analysis quality. Fig. 6 shows the results of a heart rate limits search after analyzing without a noise filter. Noisy data often triggers at a higher rate, and noisy search results may be selected as shown below for exclusion from further analysis.

In addition to verifying data quality, outlier searches can highlight areas of interest in clean, well-marked data as well. Fig. 7 shows the results from a heart rate change search. In this instance the HR Change search has returned instances of sinus pause, however, similar searches can be constructed for other derived parameters allowing for an inspection of data in areas of marked beat to beat change.

4.5. Efficient review of results

Once a search is executed, operator oversight confirms the outcome. Providing an efficient means of reviewing search results is critical to handling large datasets. In order to simplify this review process, Data Insights displays data graphically and numerically. The graphical presentation allows the user to efficiently visualize the results to assess cycle morphology and analysis mark placement. This method allows the researcher to crosscheck the arrhythmia and to ensure that in the case of ventricular complexes that it's not transient ventricular tachycardia or fibrillation (as recommended by the Lambeth Convention II guidelines(Curtis et al., 2013)). Numeric results consist of data corresponding to each search input, providing a means to validate matches. Results may be sorted by time or by any of the search inputs, permitting a targeted, systematic approach to reviewing results. A histogram of the results is also displayed, allowing the user to understand how the results are distributed throughout the dataset and identify areas where a concentration of findings may exist. If the graphical representation of a search result does not provide sufficient information, the result may be synchronized to the standard graph pages to view it in a larger context, permitting the user to view prior and following beats and make a decision about the validity of the result.

When working with 24-h datasets, cycle counts may range from 100,000 to over 800,000 beats, depending on the species. Searching such large datasets often yields results that run into the thousands. The ability to rapidly process and evaluate these search results is important to ensure study throughput. A result may be excluded from the current set of results or may be marked as invalid data, removing it from all further processing. In either case, sorting and bulk selection permits results to be evaluated rapidly.

Processing of data with Data Insights is an interactive process and it is important that search results are obtained rapidly. In the case of 29 h of canine data with approximately 160,000 beats, searches took 1–5 s depending on the number of results (using a laptop with an i7 processor and an SSD). A typical review process would involve setting up a search after which any changes to analysis, rejection of results or marking of invalid data will automatically update the search results.

Improved efficiency permits the expansion of conducting arrhythmia detection on a few cardiac cycles from multiple time points within a collection period, to include the entire collection period (Hamlin, Kijtawornrat, & Keene, 2004).

As recommended by the Lambeth Convention guidelines (II), continuous data collection is desirable for reporting arrhythmias. The ability to view continuous data for longer durations (e.g. 24 h of data) over

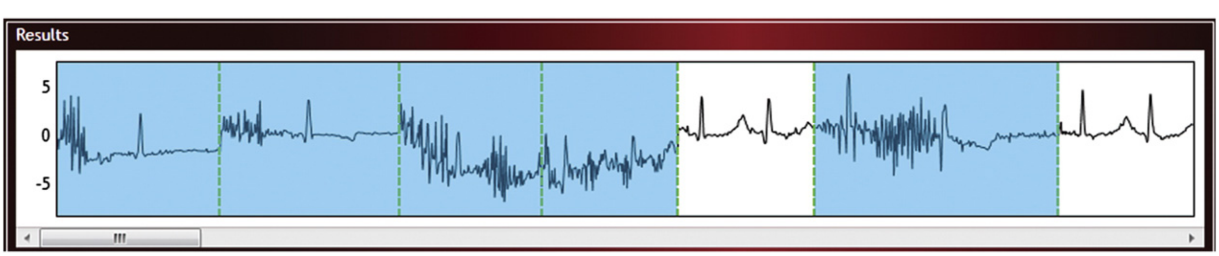


Fig. 6. Graphical results as displayed in the Data Insights Results Wave View from a heart rate limits search executed on an ECG signal from a canine. This search may be used to quickly evaluate heart rate outliers. The results highlighted in blue are examples of the signal noise induced triggering. Data Insights may be used to efficiently eliminate these sections from derived results.

Fig. 7. Graphical results as displayed in the Data Insights Results Wave View from a heart rate change search executed on an ECG signal from a canine. In this example, instances of sinus pause were located.

multiple days not only allows the user to obtain the baseline sinus rhythm and background incidences of arrhythmias for the specific animal, but it also increases the likelihood of detecting the low incidence of various arrhythmias.

5. Conclusion

Data Insights provides an efficient method for locating, presenting, and reporting on data patterns and abnormalities for comprehensive, consistent results.

Traditional methods for locating and classifying arrhythmias relied on manual review of all ECG complexes in a dataset. This was an inefficient process for studies with large amounts of data and introduced variability in results between analysts. Due to this challenge, a number of tools have been designed to improve the process of data review and analysis for ECG signals and arrhythmia assessment. When using Data Insights for arrhythmia detection, it provides a more comprehensive assessment, consistent with published literature and requires less time than traditional methods. Data Insights searches permit all data collected to be analyzed, allowing researchers to quantify background and drug-induced incidences of arrhythmias for a more robust assessment of proarrhythmic effects. Data Insights is also expected to improve reproducibility of results by reducing inter-analyst variability through the deployment of standard Data Insights searches across analysis workstations. Based on the results presented, Data Insights software provides a reliable method to accurately locate and present potential arrhythmias for further adjudication. New searches may be defined by users to address additional search targets such as Atrial Fibrillation, Mobitz I and II and Torsades de Pointes. Searches for some of these targets are under evaluation; as DSI qualifies new searches they will be made available to users.

Acknowledgements

N. Bari Olivier, D.V.M., Ph.D., DACVIM, was the veterinary cardiologist who performed the over read of the data used in the internal qualification of Data Insights. The authors would also like to thank Charles River Laboratories and especially Henry Holzgrefe, Ph.D., Kevin Norton and Robert Kaiser, Ph.D. for sharing their expertise and data.

References

Authier, S., Pugsley, M. K., Troncy, E., & Curtis, M. J. (2010). Arrhythmogenic liability screening in cardiovascular safety pharmacology: Commonality between non-clinical safety pharmacology and clinical thorough QT (TQT) studies. *Journal of Pharmacological and Toxicological Methods*, *62*(2), 83–88.

Chui, R. W., Derakhchan, K., & Vargas, H. M. (2012). Comprehensive analysis of cardiac arrhythmias in telemetered cynomolgus monkeys over a 6 month period. *Journal of Pharmacological and Toxicological Methods*, *66*(2), 84–91.

Cools, F., Janssens, S., Vanlommel, A., Teisman, A., Towart, R., & Gallacher, D. J. (2011). ECG arrhythmias in non-implanted vs. telemetry-implanted dogs: Need for screening before and sufficient recovery time after implantation. *Journal of Pharmacological and Toxicological Methods*, *64*(1), 60–67.

Curtis, M. J., Hancox, J. C., Farkas, A., Wainwright, C. L., Stables, C. L., Saint, D. A., ... Walker, M. J. A. (2013). The lambeth conventions (II): Guidelines for the study of animal and human ventricular and supraventricular arrhythmias. *Pharmacology and Therapeutics*, *139*(2), 213–248.

Ettinger, S. J., & Feldman, E. C. (2009). *Textbook of veterinary internal medicine*. Elsevier Health Sciences.

Gauvin, D. V., Tilley, L. P., Smith, F. W. K., & Baird, T. J. (2006). Electrocardiogram, hemodynamics, and core body temperatures of the normal freely moving cynomolgus monkey by remote radiotelemetry. *Journal of Pharmacological and Toxicological Methods*, *53*(2), 140–151.

Gauvin, D. V., Tilley, L. P., Smith, F. W. K., & Baird, T. J. (2009). Spontaneous cardiac arrhythmias recorded in three experimentally- and drug-naive laboratory species (canine, primate, swine) during standard pre-study screening. *Journal of Pharmacological and Toxicological Methods*, *59*(2), 57–61.

Hamlin, R. L., Kijtawornrat, A., & Keene, B. W. (2004). How many cardiac cycles must be measured to permit accurate RR, QT, and QTc estimates in conscious dogs? *Journal of Pharmacological and Toxicological Methods*, *50*(2), 103–108.

Miller, R. H., Lehmkuhl, L. B., Bonagura, J. D., & Beall, M. J. (1999). Retrospective analysis of the clinical utility of ambulatory electrocardiographic (Holter) recordings in syncopal dogs: 44 cases (1991–1995). *Journal of Veterinary Internal Medicine / American College of Veterinary Internal Medicine*, *13*(2), 111–122.

Nelson, R. W., & Couto, C. G. (2008). *Small animal internal medicine*. Elsevier Health Sciences.

Pettit, S. D., Berridge, B., & Sarazan, R. D. (2010). A call for more integrated cardiovascular safety assessment. *Journal of Pharmacological and Toxicological Methods*, *61*(1), 1–2.

Piccini, J. P., Whellan, D. J., Berridge, B. R., Finkle, J. K., Pettit, S. D., Stockbridge, N., ... Krucoff, M. W. (2009). Current challenges in the evaluation of cardiac safety during drug development: Translational medicine meets the Critical Path Initiative. *American Heart Journal*, *158*(3), 317–326.

Silverstein, D., & Hopper, K. (2014). *Small animal critical care medicine*. Elsevier Health Sciences.

Smith, F. W. K., Tilley, L. P., Oyama, M. A., & Sleeper, M. M. (2016). *Manual of canine and feline cardiology* (5th ed.). St. Louis: Elsevier.