Extended electrocardiographic monitoring in patients on chronic haemodialysis and after renal transplantation

Scott Gareth Lee-Jones
LJNSCO001

a dissertation submitted for the degree of
Master of Medicine (MMED) in Medicine

Department of Medicine Faculty of Health Sciences University of Cape Town

Supervisors

A/Prof Ashley Chin
Division of Cardiology, Faculty of Health Sciences, University of Cape Town
Dr Charle Viljoen
Division of Cardiology, Faculty of Health Sciences, University of Cape Town
A/Prof Erika Jones
Division of Nephrology and Hypertension, Faculty of Health Sciences, University of Cape Town
Prof Brian Rayner
Division of Nephrology and Hypertension, Faculty of Health Sciences, University of Cape Town

Submitted on 5th April 2022

Revision submitted 10th August 2022

Dedication

To my darling wife, Sarah. Without your love and support I would not have completed this task. Thank you for keeping me grounded and sane. Thank you for insisting that I can be greater than I believe myself to be.

Plagiarism Declaration

"This thesis/dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software) and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor."

Name: Scott Gareth Lee-Jones

Student number: LJNSCO001

Signature:

Date: 30/03/2022

Acknowledgements

My greatest thanks must go firstly to Charle Viljoen, who first approached me to start this MMED project. Despite your own prodigious undertakings, you have been unfailingly enthusiastic, present and supportive. I have learnt many lessons both in how to conduct research but also in how to conduct life.

Ashley Chin and Erika Jones have also been available with expert advice, assistance and encouragement. Brian Rayner's final edits and advice were invaluable.

Contributions

Scott Lee-Jones was responsible for protocol writing, data collection and manuscript writing.
Charle Viljoen assisted with protocol development, statistical analysis of data, review and editing.
Ashley Chin, Erika Jones and Brian Rayner contributed to review and editing.

Format

This dissertation is presented in the publication-ready format as per the instructions from the University. The targeted journal for submission is the International Journal of Cardiology and the intention is to submit once feedback from the MMED assessment process has been incorporated into the final manuscript.

Table of Contents

Publication-ready manuscript

Title

Extended electrocardiographic monitoring in patients on chronic haemodialysis and after renal transplantation

Authors

Scott Gareth Lee-Jones[1], Charle André Viljoen[2], Erika SW Jones[3], Brian Rayner[3], Ashley Chin[2].

Affiliations

(1) University of Cape Town, Department of Medicine, Cape Town, South Africa

(2) University of Cape Town, Division of Cardiology, Cape Town, South Africa

(3) University of Cape Town, Division of Nephrology and Hypertension, Cape Town, South Africa

All authors mentioned above take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Keywords

arrhythmias, CKD, loop recorder, dialysis, renal transplantation

Structured Abstract

Background

Chronic Kidney Disease (CKD) and chronic haemodialysis are associated with cardiovascular disease. Despite the increased risk of sudden cardiac death, few studies to date have described the burden of arrhythmias in this population. The aim of this study was to determine the prevalence, type and timing of arrhythmias by means of implantable loop recorder (ILR) monitoring in patients with CKD on chronic haemodialysis.

Methods

In this prospective cohort study, ILR's were implanted in twenty patients with CKD on the Renal Replacement Programme at Groote Schuur Hospital in Cape Town. Clinical, electrocardiographic and echocardiographic parameters were collected. We reviewed ILR recordings obtained between August 2015 and July 2018 and analysed arrhythmic events in relation to clinical parameters and temporal relation to dialysis sessions.

Results

In this cohort of 17/20 patients (1 died prior to ILR download and 2 lost to follow-up), the median age was 38 years (IQR 27.5 – 45) and left ventricular ejection fraction (LVEF) 62% (48 – 73). Clinically significant arrhythmias included atrioventricular (AV) block (n=24), atrial fibrillation (n=12) and non-sustained ventricular tachycardia (n=2). Most (57.4%) arrhythmic events occurred in the long interdialytic period between dialysis sessions. One patient with high degree AV block detected by ILR received a permanent pacemaker. Arrhythmic events were less prevalent after renal transplantation (6/17 during study period).

Conclusion

We have demonstrated that there is potential clinical utility of ILR monitoring in this population, which have a high risk of largely asymptomatic, clinically significant arrythmias. Larger studies are required to validate our findings.

Introduction

Chronic kidney disease (CKD) is a major contributor to the global health burden with an age-standardised global prevalence of CKD stages 1 – 5 in adults aged 20 and older of 10.4% in men and 11.8% in women.[1] The combination of rapid urbanisation, the Human Immunodeficiency Virus (HIV) epidemic and increasing rates of non-communicable diseases, make people in sub-Saharan Africa especially vulnerable to kidney disease with an overall prevalence of 13.9%.[2] CKD is a strong independent risk factor for adverse cardiovascular and mortality outcomes in the general population.[3] This is particularly relevant in haemodialysis (HD) patients where cardiovascular mortality including sudden cardiac death (SCD) constitutes approximately a quarter of all deaths.[4, 5] SCD is temporarily related to the timing of a HD session with an increased risk 12 hours after a dialysis session and at the end of a long interdialytic period (LIDP).[6]

CKD is also associated with atrial fibrillation (AF) with a prevalence in CKD patients of 11.6% and is associated with an increase in mortality and stroke .[7] To date, there is little data on the frequency and types of arrythmias that occur in patients receiving chronic HD. Wong *et al.* reported severe bradycardia and asystole as causes of unexpected SCD in their cohort of CKD patients on haemodialysis particularly after the long LIDP.[8] Bradycardias were the most common events found in a study by Roy-Chaudhury *et al*.[9] and were more likely to occur in the last 12 hours of the inter-dialytic period, especially after the LIDP.

The aim of this study was to determine the prevalence, type, timing and burden of arrhythmias by means of implantable loop recorder (ILR) monitoring in patients with CKD on the Renal Replacement programme at Groote Schuur Hospital in Cape Town. ILRs are able to record the cardiac rhythm and this provided an opportunity to study the prevalence, type, timing and burden of arrhythmias in this cohort of HD patients. To the best of our knowledge this is the first study to investigate arrhythmias in patients with CKD in this manner in Sub-Saharan Africa. Due to the strict eligibility criteria for the Renal Replacement programme, the state-funded dialysis population are younger and have fewer comorbidities.

Methods

Study Design and Patient Recruitment

This was a sub-study of the EPIQ trial conducted at the Divisions of Nephrology and Cardiology, Groote Schuur Hospital and University of Cape Town, South Africa. The study was approved by Human Research Ethics Committee of the University of Cape Town (HREC 058 / 2015).

The EPIQ (REspiration Patterns with impedance in LINQ) study, sponsored by Medtronic, was an interventional, prospective, non-randomised, single centre study undertaken at our HD centre.[10] The purpose of EPIQ was to evaluate the use of subcutaneous impedance measured by Medtronic Reveal LINQ™ implantable loop recorders (ILRs) as a respiratory rate monitor. The EPIQ study results have not been published as yet.

All arrhythmic events recorded by ILRs between the 1st of August 2015 and the 31st July 2018 were documented and analysed in relation to timing of haemodialysis, clinical parameters, electrocardiographic and echocardiographic findings. These records were retrospectively obtained from the patient's file.

Eligibility criteria

All patients who were enrolled in the EPIQ study were included in this sub-study. Briefly, they had be 18 years and older receiving chronic haemodialysis. Patients were excluded if they had pre-existing cardiac arrhythmias including atrial fibrillation, significant respiratory disease such as chronic obstructive airways disease or pulmonary hypertension, severe systolic heart failure (NYHA IV) or acute infection.

Chronic haemodialysis

Dialysis at Groote Schuur Hospital is performed three times a week for a four-hour period for all patients. Adequacy is evaluated using both the Kt/V ratio and the urea-reduction ratio. Adequacy targets are 1.2 and 70%, respectively. The 8.4% bicarbonate dialysis solution is used for the

majority of patients and with electrolyte concentrations of calcium 1.2 mmol/l, potassium 2 mmol/l, sodium 138 mmol/l, and magnesium 0.5 mmol/l.

Renal Replacement Programme

Patients with CKD who are receiving haemodialysis or peritoneal dialysis who are on the renal transplantation waiting list. In the Western Cape in South Africa, provincially based criteria for accepting patients onto a government-funded chronic renal replacement programme are based on a category system. Patients are divided into 3 categories; Category 1 includes patients who must be accepted for treatment, Category 2 includes patients who will be accepted depending on the availability of space on the programme and Category 3 includes patients who will be excluded.[11] The criteria are based on suitability for transplantation. These criteria are ethically endorsed and adhered to.

Implantable loop recorder

Participants in the EPIQ study were implanted with the Medtronic Reveal LINQ™ ILR. The Reveal LINQ™ is a leadless device implanted subcutaneously in the left 4th intercostal space. Two electrodes on the body of the device continuously monitored the patient's heart rhythm. This device can store up to 30 minutes of ECG recordings of patient-activated episodes and up to 27 minutes of ECG recordings of the automatically detected arrhythmias (see definitions below). The device could be activated by the patient with a hand-held device if the patient experienced any symptoms which was then recorded by the ILR as a "patient-activated episode".

The ILR automatically recorded arrhythmias defined as an "automatically detected episode" as follows:

Tachycardia > 158bpm

Bradycardia <30bpm

Pause > 3 seconds

Atrial fibrillation/Atrial tachycardia (based on a standard device algorithm)

As part of routine clinical care of patients with ILRs, these patients were monitored for arrhythmias by means of regular interrogations by the division of Cardiology, Groote Schuur Hospital in Cape Town. These occurred on a 3 monthly basis or more frequently if patients reported any symptoms.

All arrhythmic events were adjudicated by a specialist Cardiologist and electrophysiologist (AC) and fellow (CV) from the division of Cardiology at Groote Schuur Hospital in Cape Town. An adjudicated arrhythmia was defined as any episode of sinus tachycardia, atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular arrhythmia, asystole and heart block.

Arrythmia event timing definitions

The occurrence of an arrhythmia was categorised according to its relation to the timing of dialysis, i.e.,1) the peri-haemodialysis period and 2) the interdialytic period (IDP) as has been previously reported.[8] The peri-haemodialysis period was further subdivided into the 8 hours before a dialysis session (pre-HD), the 4 hours during a haemodialysis session (intra-HD) and the 12 hours post HD session (post-HD). HD is routinely done thrice weekly for 4 hours. The short IDP (SIDP) was the 48-hour period between dialysis sessions and the long IDP (LIDP) was the 72-hour period between dialysis sessions.

Statistical analysis

Data were collected on Research Electronic Data Capture (REDCap Version 7.5.2), a secure electronic database hosted by the University of Cape Town.[12] Data from REDCap were exported to Stata (Version 14.2, Stata Corp, College Station, TX, USA) for statistical analysis. Descriptive statistics were used to summarise data. Continuous variables were summarised as medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared with Chi-squared or Fisher exact test. A p-value of <0.05 was interpreted as statistically significant.

Results

Demographic and clinical characteristics

Twenty participants were enrolled in the EPIQ study and were included in this sub-study. Arrhythmic data were obtained from 17 of the 20 participants. Two EPIQ participants were lost to follow-up and did not have scheduled ILR downloads. One participant demised due to complications of sepsis (unrelated to the ILR insertion) early in the study period.

The median age of participants was 38 years (27.5– 45) and 8 (47.1%) were female. (Table 1) Hypertension was the cause of CKD in 11 (64.7%) patients, chronic glomerulonephritis in 5 (29.4%) and hypertension together with diabetes in 1 (5.9%) patient. The median duration on maintenance dialysis prior to the study period was 28 (16 – 55) months. Co-morbid hypertension was present in 16 (94.1%), mild heart failure (NYHA II) in 7 (41.2%) and diabetes in 2 (11.8%) participants. Vascular access was via fistula in 11 (64.7%) and permanent catheter in 5 (29.4%).

All 17 participants underwent a baseline 12-lead ECG (Table 1). All participants were in sinus rhythm with a median heart rate of 72 (66 – 81) beats per minute, median PR duration of 158 (143 – 186) milliseconds (ms) and a median QRS duration of 92 (81 – 98) ms. No one had a prolonged QRS duration and no bundle branch blocks were present. The calculated QT interval was prolonged in 6 participants (35.3%) with a median duration of 435 (415 – 461.5) ms, 1 was in a male participant and 5 were in female participants. Left atrial enlargement was present in 5 (29.4%) and voltage criteria by Sokolow-Lyon for left ventricular hypertrophy was present in 7 (41.2%).

Thirteen participants had baseline echocardiograms with a median left ventricular ejection fraction (LVEF) of 62% (48 – 73) (Table 1). Only 4 (31%) had an LVEF less than 50%, the lowest recorded EF being 43%. Left atrial enlargement was present in 9 (69.2%) and left ventricular hypertrophy in 8 (61.5%). Diastolic dysfunction was present in 6 (55.6%) with grade 3 diastolic dysfunction in 4.

Arrhythmia events

A total of 3879 automatically-detected and 40 patient-activated events were recorded in 12 participants during the study period (see Figure 1). Due to the limited recording space on the ILR devices, 583 of these events had recorded electrograms (EGMs) that could be reviewed and adjudicated. Of these 583 EGMs, 155 were adjudicated to be arrhythmias.

Bradyarrhythmias

Twenty-four (15.5%) episodes of AV block were detected in 2 participants. The first participant had 9 episodes of 2:1 AV block, 3 episodes of 3:1 AV block and 4 episodes of 4:1 AV block. The ongoing episodes of high-grade AV block required prompt implantation of a permanent pacemaker. The second participant had 6 brief, intermittent episodes of complete heart block and one episode of unclassified 2nd degree heart block between January and April 2016. There was one further episode of unclassified 2nd degree heart block in December 2017 and thereafter no further episodes. A decision was made not to implant a pacemaker as the heart block had resolved. A single, brief episode of sinus arrest of only 3 seconds duration occurred within 1 hour of completing a dialysis session in 1 patient. This participant was asymptomatic and did not require a permanent pacemaker.

Tachyarrhythmias

Twelve episodes (7.7%) of paroxysmal atrial fibrillation (AF) occurred in 4 participants. The median duration of the episodes was 41417.33 (9 – 108253.3) seconds/11.5 (0.0025 – 30.07) hours, however the wide interquartile range is explained by 2 events of significant length, 364140 seconds (101.15 hours) and 129960 seconds (36 hours) respectively, in 2 different participants. Despite meeting criteria for giving oral anticoagulation, the decision was made in both instances that the potential harm from giving oral anticoagulation outweighed potential benefit. All other events were of short duration, the longest being 1800 seconds (0.5hrs), and therefore anticoagulation was not indicated.

The 116 (74.8%) episodes of sinus tachycardia were the most common arrhythmia recorded. The ILR recorded that all participants were active during these events which made an atrial tachycardia very unlikely. Two episodes of non-sustained monomorphic ventricular tachycardia (VT) of 12- and 6-seconds duration occurred in a single participant. One of these episodes occurred during a dialysis session. No episodes of sustained monomorphic ventricular tachycardia or polymorphic ventricular tachycardia/ventricular fibrillation were recorded.

Six participants activated their devices to record a total of 40 "patient-activated arrythmias" however none of these were found to correlate with a true arrythmia event.

Timing of events

All patients on the Renal Replacement programme at Groote Schuur are potential renal transplant candidates. During the study period, 6 of the 17 participants were transplanted. The majority of events 148 of 155 (90.9%) occurred in those still on maintenance haemodialysis. Two atrial fibrillation episodes were observed in 1 participant post renal transplantation. No other significant arrythmias occurred after transplantation. The cumulative duration studied post-transplant was shorter at 120 months versus 420 months for those on dialysis.

Among those on chronic dialysis, events occurred most frequently in the LIDP. There were 81 (57.4%) events in the LIDP, 52 in the SIDP (36.8%) and only 7 (4.8%) during dialysis. Furthermore, within the LIDP and SIDP, 10 (41.6%) of the AV blocks including 3 episodes of complete heart block occurred at the end of these periods in the pre-dialysis period. Twenty-eight (47.4%) sinus tachycardia episodes occurred in the post-dialysis period. There were also 7 (58.3%) episodes of atrial fibrillation in the post-dialysis period.

T wave oversensing and R wave undersensing

The discrepancy between detected number of events and true arrhythmias related to misidentification of an arrythmia by the device due to either T wave oversensing, R wave undersensing or artefact. There were 283 (48.5%) events of T wave oversensing and 53 (9.1%) of R wave undersensing directly reviewed on electrogram. The ILR incorrectly identified these as

either sinus tachycardia or atrial fibrillation. Figure 2 L demonstrates an example of T wave oversensing.

Discussion

This study was designed to report the prevalence, type, timing and burden of arrhythmias in patients on maintenance haemodialysis at Groote Schuur Hospital detected by ILR monitoring. The main findings of the study were: 1) arrhythmias occurred in 31% of patients, 2) the most common arrhythmias were atrial fibrillation and AV block, 3) these events were mostly likely to occur in the interdialytic period with more events occurring in the LIDP than the SIDP and 4) arrhythmias were less common after kidney transplant.

The use of ILRs in prior studies have demonstrated that bradyarrhthymias occur more commonly than previously expected in patients on haemodialysis and are potentially causative in SCD. [9, 13, 14] The AV blocks detected in our study mostly occurred in the LIDP and also towards the end of this period. This was consistent with findings from previous studies of the temporal relationship of arrythmias by Wong *et al.* and Roy-Chaudery *et al*.[8, 9] A systematic review by Roberts *et al.* reported an all-cause mortality of a calculated rate of 0.14 deaths per patient-year of study.[15] An ILR download was not performed posthumously on the single patient that died in our study. This patient died soon after a kidney transplant of overwhelming sepsis. The lower number of deaths in our study may be related to the exclusion of patients from the study with significant heart disease.

In contrast to prior studies, sinus node dysfunction was uncommon with only 1 patient in this study having a single episode of sinus arrest lasting 3 seconds. The PRETRANSPLANT study showed that patients with bradyarrhythmias were significantly older (62.7 ± 57.7 years vs 57.7 ± 9.1 years) and had a higher prevalence of coronary artery disease.[16] Our much younger median age of 38 years (27.5– 45) and the absence of documented coronary artery disease may explain why bradyarrhythmias occurred infrequently.

There is a heightened risk of mortality and admission for cardiovascular disease after the LIDP.[17] There appears to be conflicting evidence to explain the increase in risk: electrolyte abnormalities, dialysate composition and fluid shifts during dialysis have been implicated. Some have reported that low potassium and calcium dialysate baths (<2mEq/L) are associated with SCD. [18, 19] However, Roy-Chaudery *et al.* noted that higher calcium dialysate (>2.5mEq/l) and high serum sodium was

independently associated with clinically significant arrythmias. Wong *et al.* noted that the pre-dialysis potassium was higher at the end of the LIDP than the SIDP and that the mean body weight change was greater in the LIDP than the SIDP, but they did not analyse the association with arrhythmias.[8] More recently Tumlin *et al.* showed that intradialytic change in potassium and weight were not significantly associated with arrythmias[20] and Raautavara *et al.* showed no association with any serum electrolyte or dialysate bath parameters.[14] Similar to previous studies we found that arrhythmia risk was higher in the LIDP but are unable to link biochemical abnormalities and fluid balance as these data were not collected as part of the study.

The use of ILR monitoring has been shown to be effective in correlating symptoms with rhythm abnormalities and affects management. [21] Our study did not confirm any direct symptom correlation which suggests that many patients experience symptoms that are not directly related to an arrhythmia. This supports the use of ILR to exclude an arrhythmia in a significant proportion of patients.

Diagnosis of paroxysmal arrhythmias like AV block and paroxysmal AF can be challenging. This study shows that ILR improves the ability to detect arrhythmias and can change management. The detection of a clinically significant AV block and referral for permanent pacemaker in this study highlights the potentially beneficial role of ILR's in patients receiving long term HDs. Sacher *et al.* concluded that ILR monitoring was indicated in HD patients prone to significant conduction disorders, ventricular arrythmias, or atrial fibrillation or flutter.[22] Our study was too small to determine who will benefit the most from ILR's.

Atrial fibrillation rates are reportedly higher than the normal population in ILR studies in patients on haemodialysis. [15] This is understandable because the commonest comorbidities associated with AF include hypertension (which was present in 94.1% of this population), heart failure and diabetes, all independent of haemodialysis and CKD.[23] Roy-Chaudery *et al*. noted that AF frequency was highest during each dialysis session but decreased over the next 24-36 hours.[9] However, Wong *et al.* reported that AF was most common at the end of the LIDP[8] . Our study found the majority of AF events occurred in the post-dialysis period. The prevalence of AF that occurred (23.5%) in our study is much higher than the estimated prevalence in the general adult

population of 2 – 4%[24] however it is lower than the rates in above mentioned ILR studies of >40%.[8, 9]

Sinus tachycardia is the most commonly detected rhythm in clinical practice.[25] Similarly, sinus tachycardia was the most commonly detected rhythm in this study. It is not possible to comment whether these represent appropriate or inappropriate sinus tachycardias, however the lack of correlating symptoms self-recorded by the participants, as well as the documented shifts in fluid together with changes in blood pressure, suggest that these are likely appropriate physiological responses. Sinus tachycardia in the post-dialysis period is most likely an appropriate physiological response to the change in volume status. Ventricular arrythmias are reportedly uncommon, with an annualized rate of 0.05 per patient per year.[15] Furthermore the ICD2 study showed that there was no significant difference in SCD in dialysis patients with implantable cardioverter defibrillators.[26]

The provision of haemodialysis in the state sector in South Africa is limited by resource availability and has strict enrolment criteria.[11] These strict criteria account for the young age and relative lack of co-morbidities in our cohort when compared to haemodialysis populations in high income settings. The average age in our study was 38.5 (27.5– 45) compared to 59.8±9.3 and 56.3± 12.2 in other studies of ILR in dialysis populations from Finland[14] and the United States together with India, respectively.[9] Previous studies of ILR in haemodialysis populations did not look at patients in this age group.[13] Furthermore, in this study diabetes was present in only 1 patient whereas in the systematic review by Roberts *et al*. it was found in 58.8% (48.5–69.2) of the average dialysis populations. Although not yet fully elucidated, the correlation between diabetes and arrythmias has been observed.[27] In particular, diabetic patients have an approximately 40% greater risk of AF compared to non-diabetic populations.[28] This may explain in part the lower detected rates of AF in our study.

There are also no data available on ILR monitoring in patients after renal transplantation. To the best of our knowledge this is the first study to observe this population. Although the period under review for the post-transplant group was considerably shorter than the haemodialysis group, the very small number of events is striking. In our study, events occurred in only one patient post-transplant, and these were not considered clinically significant. It is established that cardiovascular

disease mortality is lower post renal transplantation than those awaiting renal transplantation, although it remains higher than the general population.[29] In a large registry of Australian and New Zealand transplant patients it was shown that 50% of deaths in the first year after graft failure were cardiovascular in nature.[30]

T wave oversensing, R wave undersensing and artefact occurred in a significant number of participants. This highlights the need for careful interpretation of all EGMs recorded to confirm the presence of a true arrhythmia. Undersensing is predominantly due to variations in R wave amplitude and occurs more commonly on non-dialysis days. Oversensing relates to sudden changes in T wave morphology.[13] Under- and oversensing occurred in the majority of patients in the CRASH-ILR study investigating SCD in haemodialysis patients.[13] Our study confirms a similarly high prevalence of T wave oversensing and R wave undersensing. It is speculative that these recordings are due to electrolyte abnormalities and the presence of LVH and repolarization changes and their effects on the T waves. In a study aimed at determining ILR sensitivity to investigate undiagnosed syncopal episode in a non-CKD population, 103/284 (36.2%) of recorded episodes were found to be R wave undersensing however in contrast to our study there were no detected episodes of T wave oversensing.[31] There are reports of hyperkalaemia as a cause of T wave oversensing[32] and may point to a hypothetical explanation for this large discrepancy between CKD and non-CKD patients.

Limitations

This study is limited by the small number of patients. The storage capability of the ILR may have resulted in arrhythmic events not being detected because EGMs were not stored. There was also a high rate of false detection related to T wave oversensing and R wave undersensing, which may have contributed to filling the storage capacity of the ILR. There were also challenges with data collection with infrequent downloads occurring via the Carelink devices. The resource poor environment of many of the participants may have contributed to the poor usage of the Carelink devices.

Although the HIV prevalence in the sub-Saharan Africa is high and is associated with increased risk for CKD, there were no patients with HIV on haemodialysis included in this study and this therefore remains an unexplored area in the literature.

Conclusions

Our study confirms previous findings that significant bradyarrhythmias occur in patients on haemodialysis and most commonly at the end of the LIDP. We have also demonstrated that there is potential clinical utility of ILR monitoring in this population, which have a high risk of largely asymptomatic, clinically significant arrythmias. Larger studies are required to validate our findings.

References

1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen C-S, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney International. 2015;88(5):950-7.

2. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2014;2(3):e174-e81.

3. Weiner DE, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, et al. Cardiovascular Outcomes and All-Cause Mortality: Exploring the Interaction Between CKD and Cardiovascular Disease. American Journal of Kidney Diseases. 2006;48(3):392-401.

4. Genovesi S, Valsecchi MG, Rossi E, Pogliani D, Acquistapace I, De Cristofaro V, et al. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. Nephrology Dialysis Transplantation. 2009;24(8):2529-36.

5. Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clin J Am Soc Nephrol. 2012;7(5):765-74.

6. Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. Kidney International. 2006;69(12):2268-73.

7. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrology Dialysis Transplantation. 2012;27(10):3816-22.

8. Wong MCG, Kalman JM, Pedagogos E, Toussaint N, Vohra JK, Sparks PB, et al. Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period. Heart Rhythm. 2015;12(10):2047-55.

9. Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. Kidney Int. 2018;93(4):941-51.

10. https://clinicaltrials.gov/ct2/show/NCT02828735. [

11. Swanepoel CR, Wearne N, Okpechi IG. Nephrology in Africa—not yet uhuru. Nature Reviews Nephrology. 2013;9(10):610-22.

12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

13. Roberts PR, Zachariah D, Morgan JM, Yue AM, Greenwood EF, Phillips PC, et al. Monitoring of arrhythmia and sudden death in a hemodialysis population: The CRASH-ILR Study. PLoS One. 2017;12(12):e0188713.

14. Rautavaara J, Kerola T, Kaartinen K, Vilpakka M, Aitkoski A, Anttonen O, et al. Asystole episodes and bradycardia in patients with end-stage renal disease. Nephrol Dial Transplant. 2021.

15. Roberts PR, Stromberg K, Johnson LC, Wiles BM, Mavrakanas TA, Charytan DM. A Systematic Review of the Incidence of Arrhythmias in Hemodialysis Patients Undergoing Long-Term Monitoring With Implantable Loop Recorders. Kidney Int Rep. 2021;6(1):56-65.

16. Silva RT, Martinelli Filho M, Peixoto Gde L, Lima JJ, Siqueira SF, Costa R, et al. Predictors of Arrhythmic Events Detected by Implantable Loop Recorders in Renal Transplant Candidates. Arq Bras Cardiol. 2015;105(5):493-502.

17. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis. New England Journal of Medicine. 2011;365(12):1099-107.

18. Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int. 2011;79(2):218-27.

19. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clin J Am Soc Nephrol. 2013;8(5):797-803.

20. Tumlin JA, Roy-Chaudhury P, Koplan BA, Costea AI, Kher V, Williamson D, et al. Relationship between dialytic parameters and reviewer confirmed arrhythmias in hemodialysis patients in the monitoring in dialysis study. BMC Nephrol. 2019;20(1):80.

21. Padmanabhan D, Kancharla K, El-Harasis MA, Isath A, Makkar N, Noseworthy PA, et al. Diagnostic and therapeutic value of implantable loop recorder: A tertiary care center experience. Pacing Clin Electrophysiol. 2019;42(1):38-45.

22. Sacher F, Jesel L, Borni-Duval C, De Precigout V, Lavainne F, Bourdenx JP, et al. Cardiac Rhythm Disturbances in Hemodialysis Patients: Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters. JACC Clin Electrophysiol. 2018;4(3):397-408.

23. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-20.

24. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528.

25. Yusuf S, Camm AJ. Deciphering the sinus tachycardias. Clin Cardiol. 2005;28(6):267-76.

26. Jukema JW, Timal RJ, Rotmans JI, Hensen LCR, Buiten MS, de Bie MK, et al. Prophylactic Use of Implantable Cardioverter-Defibrillators in the Prevention of Sudden Cardiac Death in Dialysis Patients. Circulation. 2019;139(23):2628-38.

27. Grisanti LA. Diabetes and Arrhythmias: Pathophysiology, Mechanisms and Therapeutic Outcomes. Front Physiol. 2018;9:1669.

28. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol. 2011;108(1):56-62.

29. Stoumpos S, Jardine AG, Mark PB. Cardiovascular morbidity and mortality after kidney transplantation. Transpl Int. 2015;28(1):10-21.

30. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. J Am Soc Nephrol. 2020;31(12):2887-99.

31. Chrysostomakis SI, Klapsinos NC, Simantirakis EN, Marketou ME, Kambouraki DC, Vardas PE. Sensing issues related to the clinical use of implantable loop recorders. Europace. 2003;5(2):143-8.

32. Aoki K, Okajima K, Kiuchi K, Yokoi K, Teranishi J, Shimane A. A case of inappropriate implantable cardioverter defibrillator therapy induced by T-wave oversensing due to hyperkalemia. J Arrhythm. 2015;31(6):395-7.

List of Tables and Figures

Table 1 – Baseline Characteristics

		Total (n=17)	Arrythmia Detected (n=6)	No Arrythmia Detected (n=11)	p-value
Age (years)	Median (IQR)	38.0 (27.0-45.0)	31.0 (24.0-38.0)	44.5 (40.0-48.0)	0.044
Cause for CKD					
Hypertension	N (%)	12 (70.6)	8 (72.7)	4 (66.7)	0.79
Diabetes Mellitus	N (%)	1 (5.9)	1 (9.1)	0 (0.0)	0.45
Glomerulonephritis	N (%)	5 (29.4)	3 (27.3)	2 (33.3)	0.79
Co-morbidities					
Heart Failure	N (%)	7 (41.2)	4 (36.4)	3 (50.0)	0.59
Medications					
Atenolol	N (%)	9 (52.9)	5 (45.5)	4 (66.7)	0.40
Carvedilol	N (%)	4 (23.5)	2 (18.2)	2 (33.3)	0.48
Enalapril	N (%)	4 (23.5)	2 (18.2)	2 (33.3)	0.48
Losartan	N (%)	6 (35.3)	4 (36.4)	2 (33.3)	0.90
Baseline ECG					
LA enlargement	N (%)	5 (29.4)	3 (27.3)	2 (33.3)	
PR interval (MS)	Median (IQR)	158.0 (146.0-184.0)	158.0 (140.0-184.0)	160.0 (152.0-188.0)	0.72
QRS width (ms)	Median (IQR)	92.0 (82.0-94.0)	90.0 (82.0-94.0)	94.0 (80.0-104.0)	0.45
LVH	N (%)	7 (41.2)	5 (45.5)	2 (33.3)	0.63
QTc (ms)	Median (IQR)	442.6 (416.3-459.4)	442.6 (416.3-459.4)	438.6 (399.9-494.6)	0.84
Echocardiogram					
LVEF (%)	Median (IQR)	62.0 (48.0-73.0)	58.5 (47.0-67.5)	70.0 (65.0-74.0)	0.12
LA enlargement	N (%)	9 (69.2)	6 (75.0)	3 (60.0)	0.57

CKD, chronic kidney disease; LA, left atrium; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction.

Table 2 – Characteristics of Arrhythmias

	Sinus tachycardia n = 116	AF n = 12	NSVT n = 2	SND n = 1	Atrioventricular block				
					2:1 AVB n = 9	3:1 AVB n = 1	4:1 AVB n = 4	Unclassified n = 4	3rd degree AVB n = 6
Timing of arrhythmia									
Related to dialysis									
Pre dialysis	11 (9.48%)	2 (16.67%)	0	0	4 (44.44%)		3 (75%)		3 (50%)
During dialysis	4 (3.45%)	0	1 (50%)	0	0				
Post dialysis	28 (47.41%)	7 (58.33%)	0	1 (100%)	0				1 (16.67%)
Between dialysis sessions	61 (52.59%)	1 (8.33%)	1 (50%)	0	5 (55.56%)	1 (100%)	1 (25%)	4 (100%)	2 (33.33%)
Interdialytic period									
SIDP	38 (36.54%)	7 (70%)	1 (50%)	0	1 (11.1%)	0	2 (50%)	2 (50%)	1 (16.67%)
LIDP	61 (58.65%)	3 (30%)	0	1 (100%)	8 (88.89%)	1 (100%)	2 (50%)	2 (50%)	4 (66.67%)
During Dialysis	5 (4.81%)	0	1 (50%)		0	0	0	0	1 (16.67%)
After renal transplant	12 (10.34%)	2 (16.67%)							

AF, atrial fibrillation; AVB, atrioventricular block; NSVT, non-sustained ventricular tachycardia; SND, sinus node dysfunction.

Figure 1: Study flow

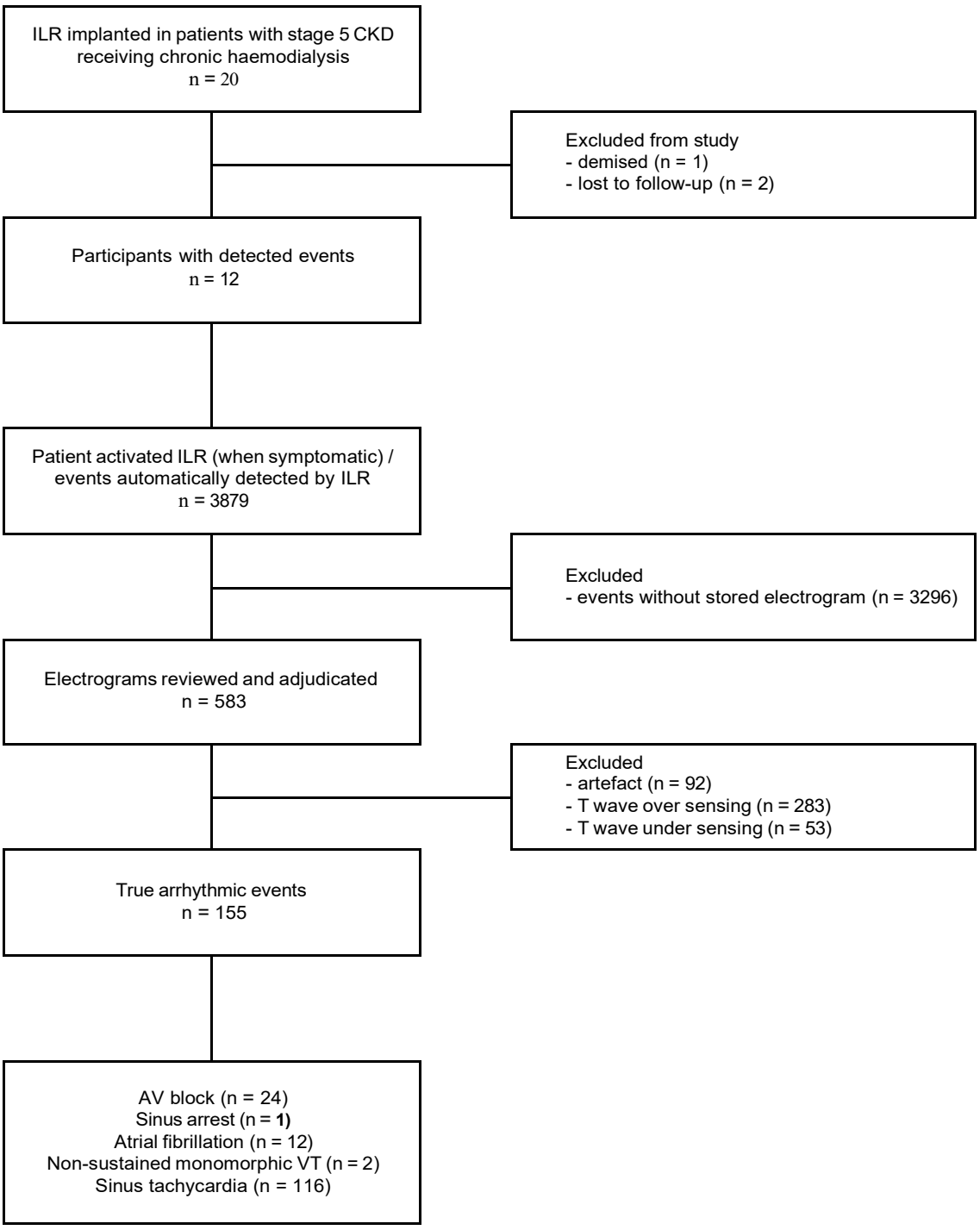
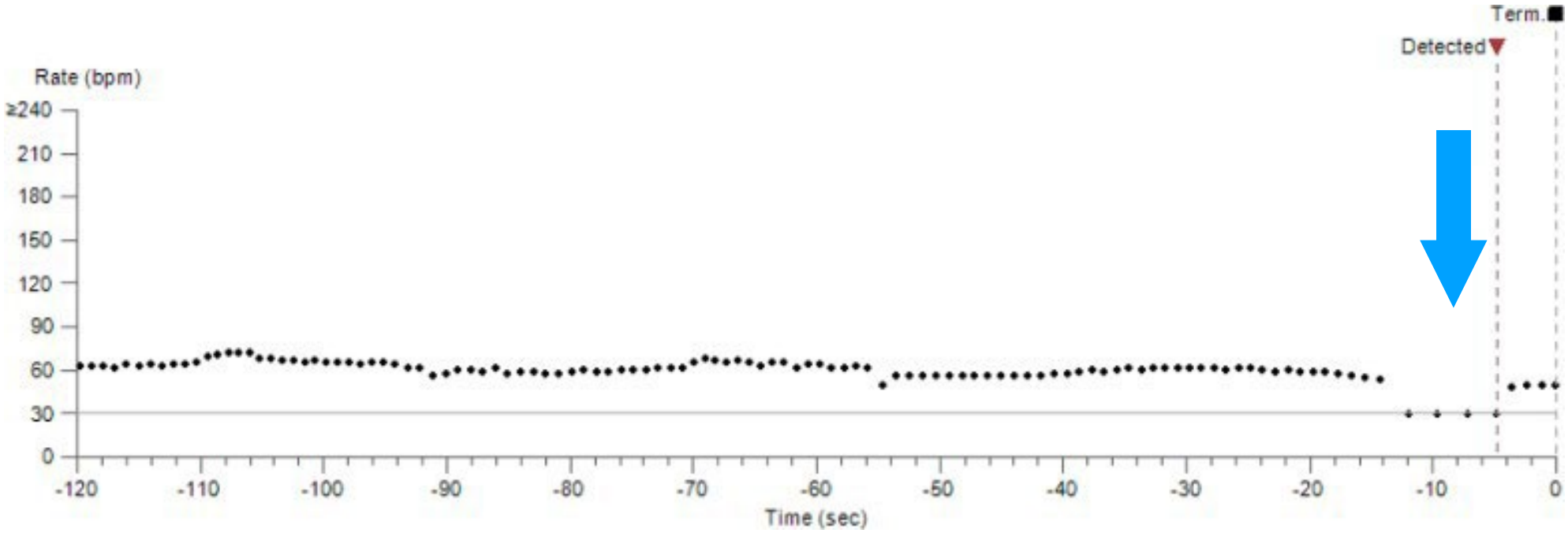
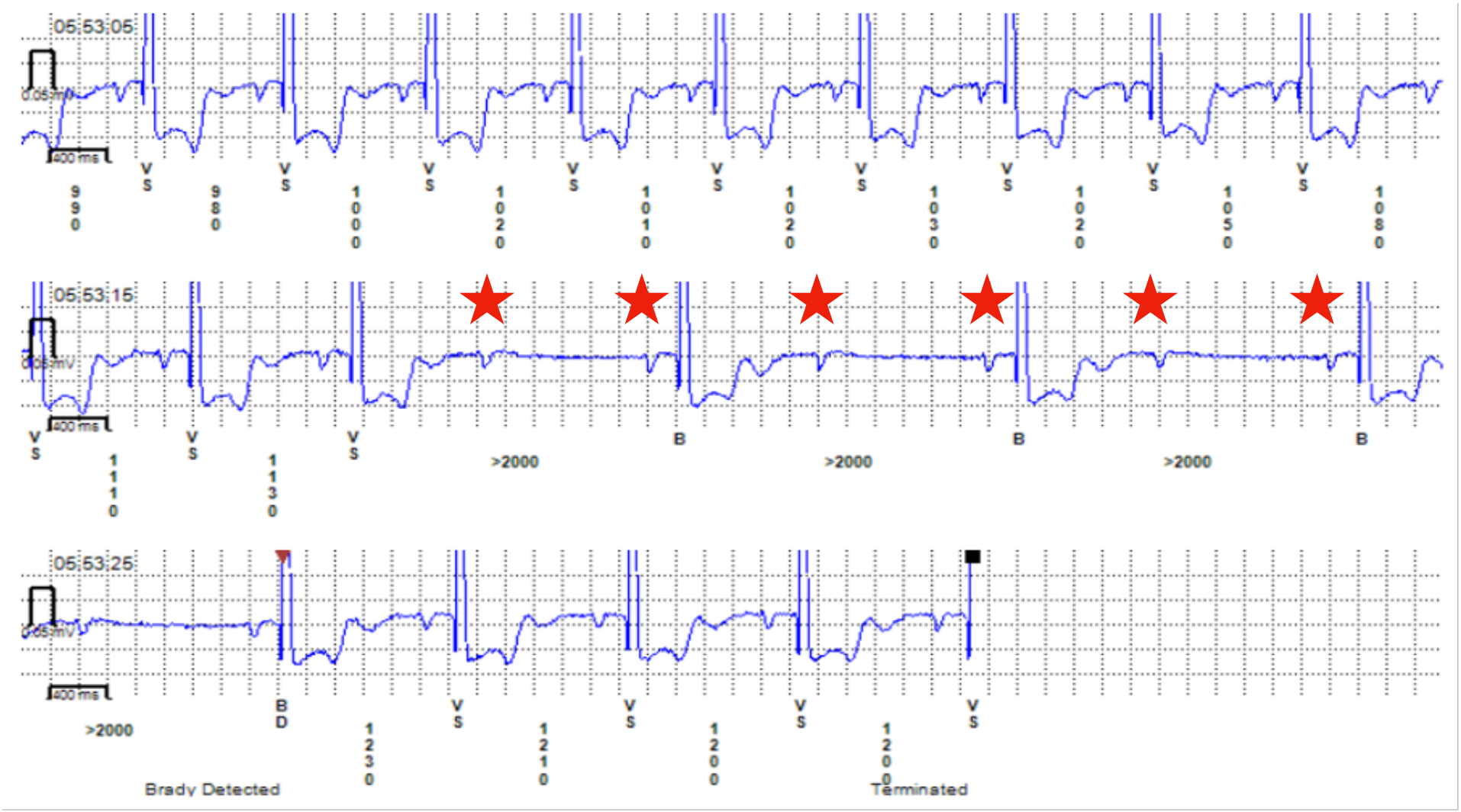


Figure 2: Implantable loop recorder electrograms

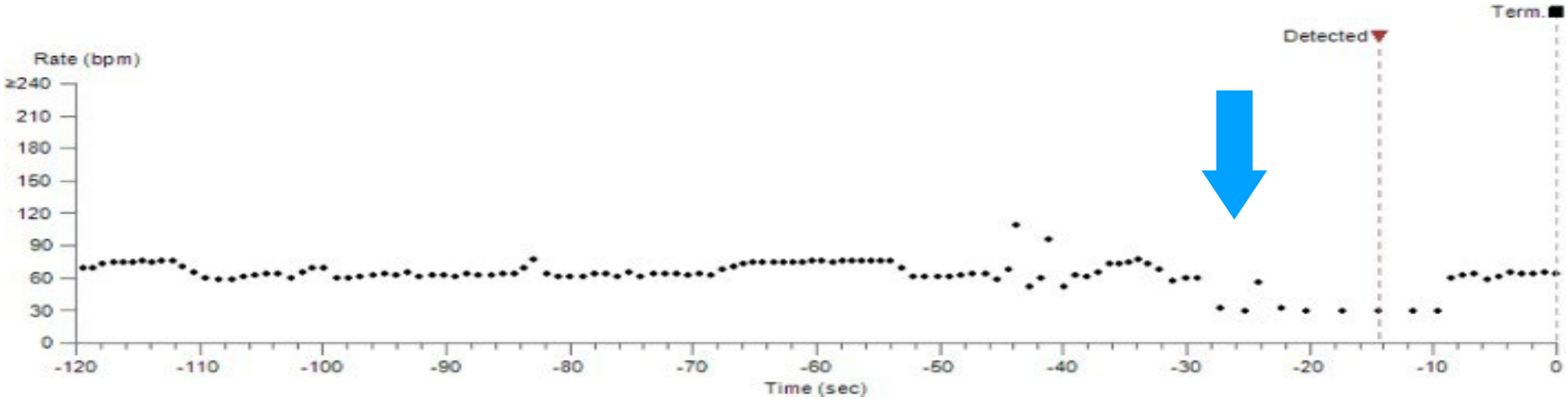
2 a



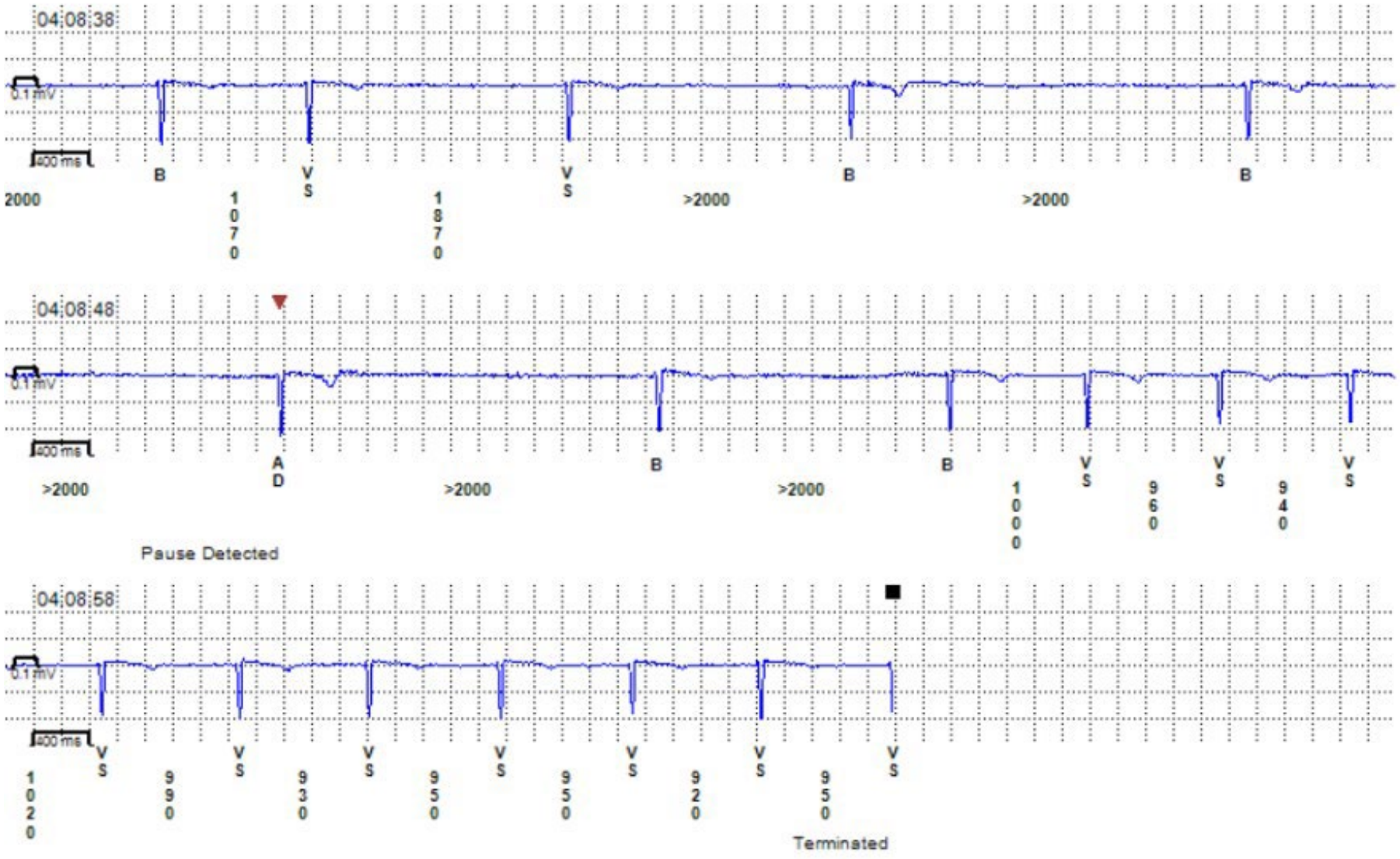
2 b


05:53:05
400 ms
VS 990 VS 980 VS 1000 VS 1020 VS 1010 VS 1020 VS 1030 VS 1020 VS 1050 VS 1080
05:53:15
400 ms
VS 1110 VS 1130 VS >2000 B >2000 B >2000 B
05:53:25
400 ms
>2000 BD 1230 VS 1210 VS 1200 VS 1200 VS
Brady Detected
Terminated

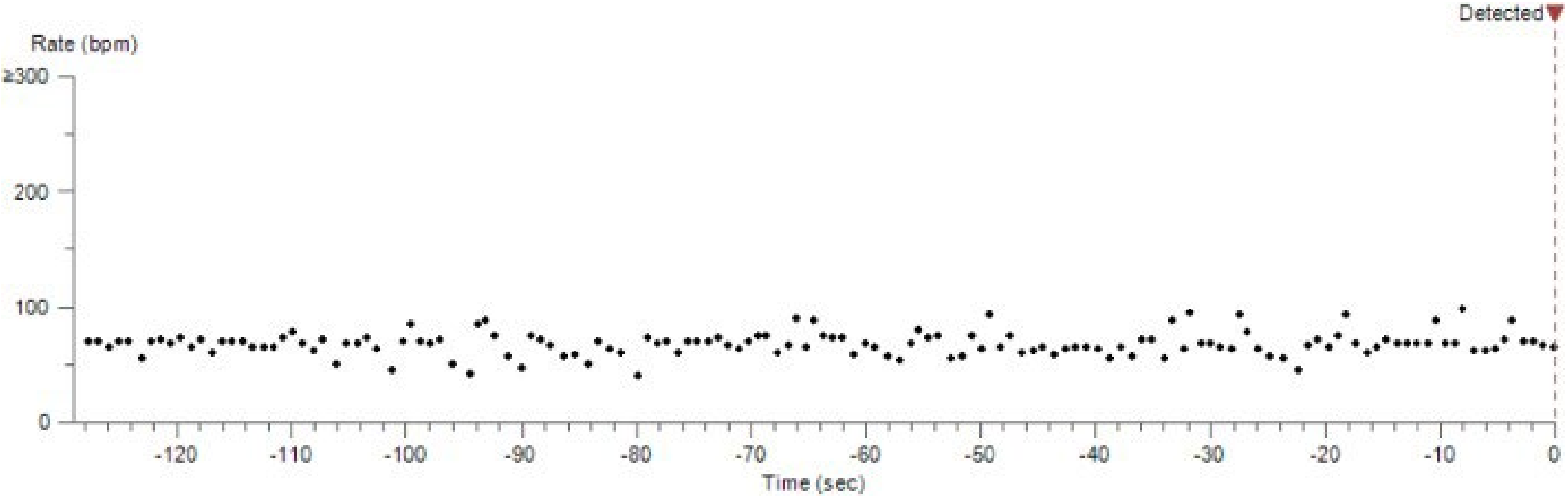
2 c


Term.
Detected
Rate (bpm)
≥240
210
180
150
120
90
60
30
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)

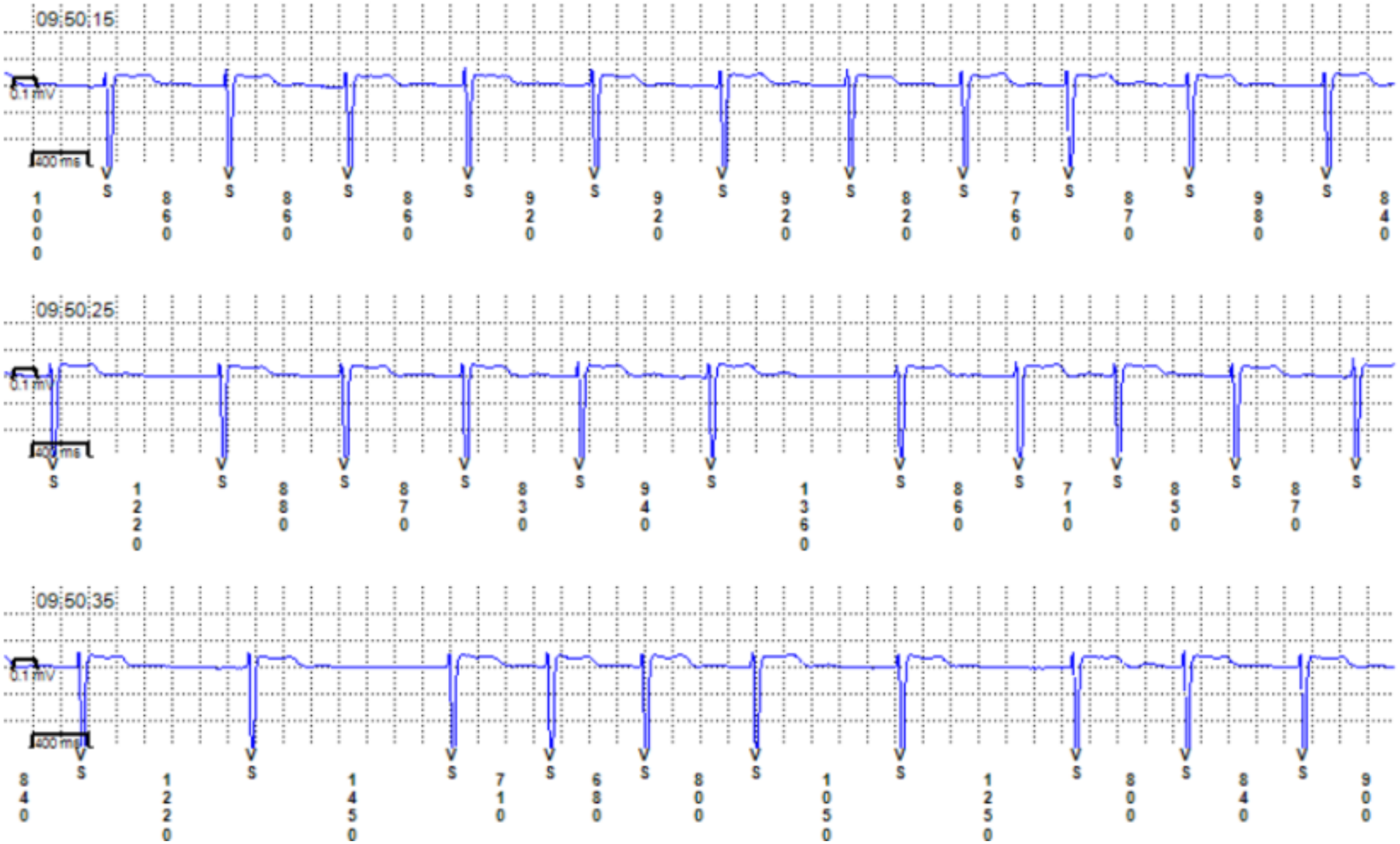
2 d


04:08:38
0.1 mV
400 ms
B
VS
VS
B
B
2000
1070
1870
>2000
>2000
04:08:48
0.1 mV
400 ms
AD
B
B
VS
VS
VS
>2000
>2000
>2000
1000
960
940
Pause Detected
04:08:58
0.1 mV
400 ms
VS
VS
VS
VS
VS
VS
VS
1020
990
930
950
950
920
950
Terminated

2 e

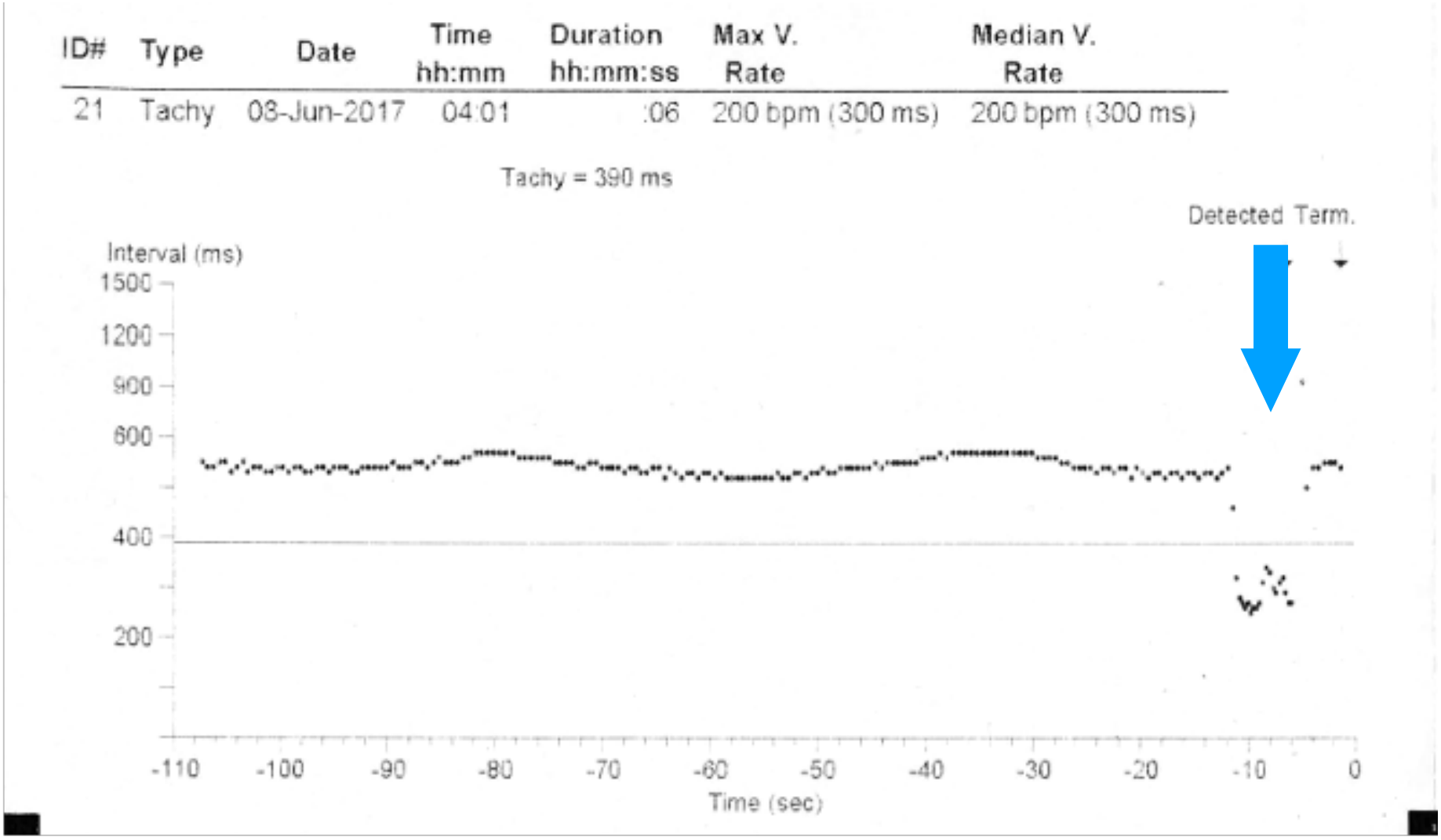

Detected
Rate (bpm)
≥300
200
100
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)

2 f

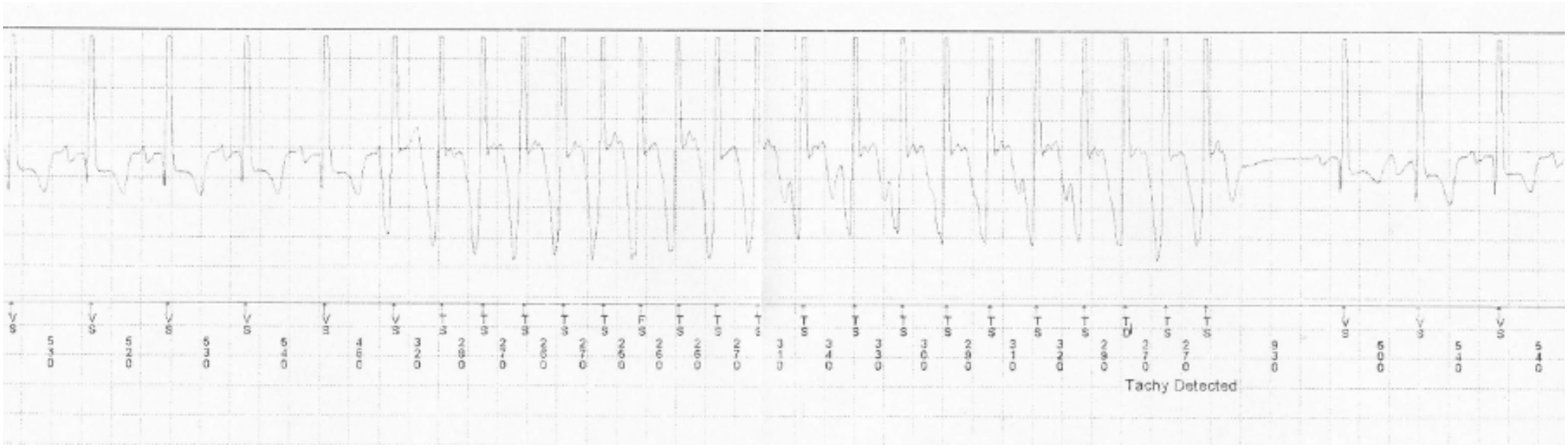


2 g

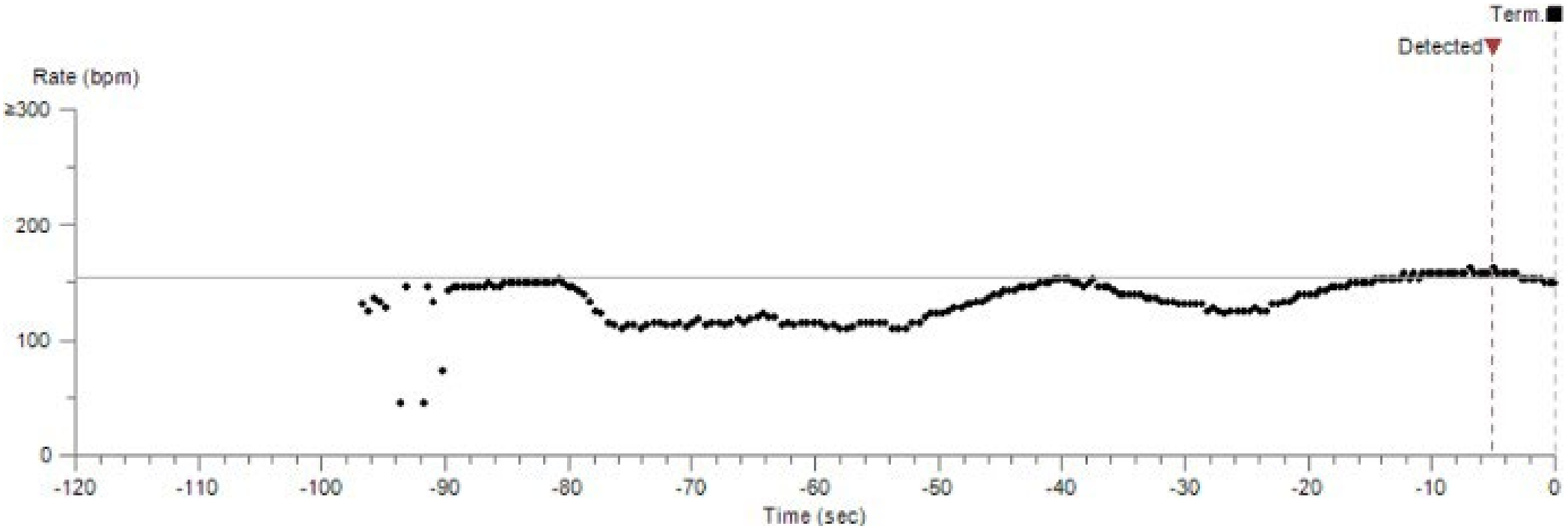
ID#	Type	Date	Time hh:mm	Duration hh:mm:ss	Max V. Rate	Median V. Rate
21	Tachy	08-Jun-2017	04:01	:06	200 bpm (300 ms)	200 bpm (300 ms)



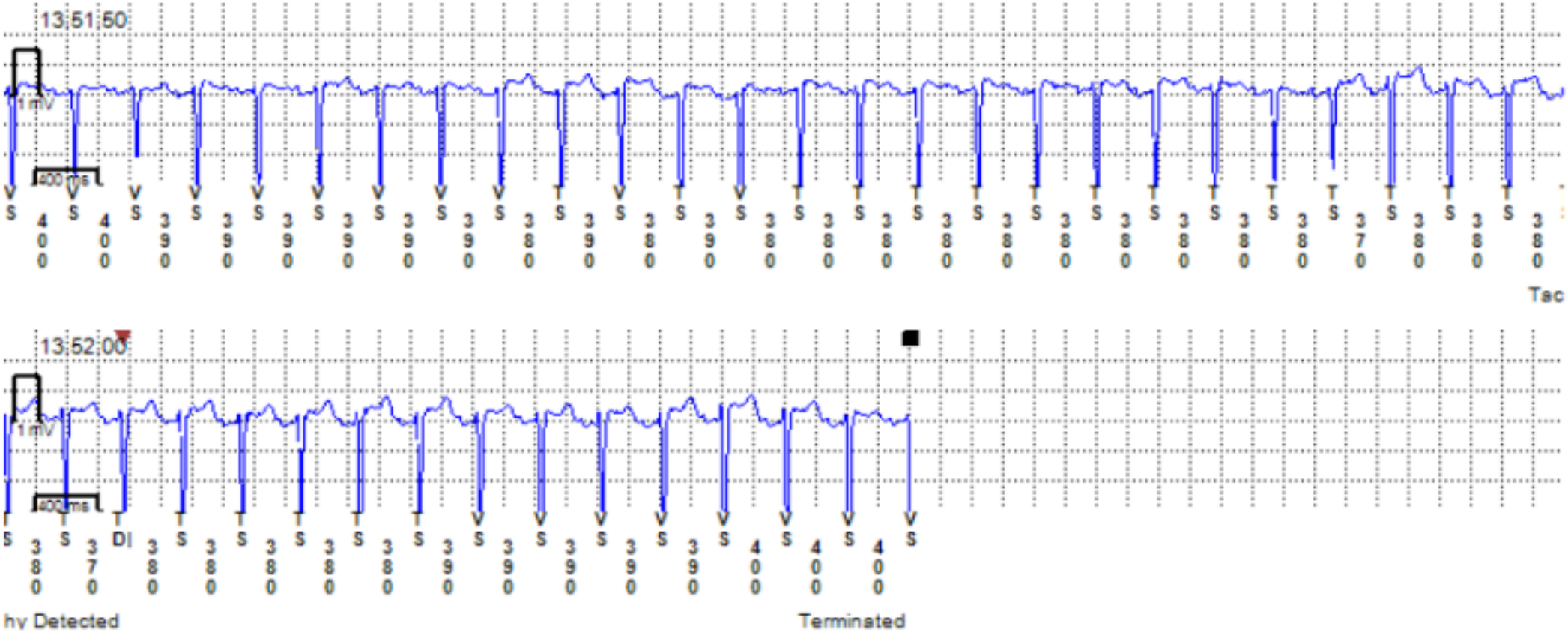
2 h



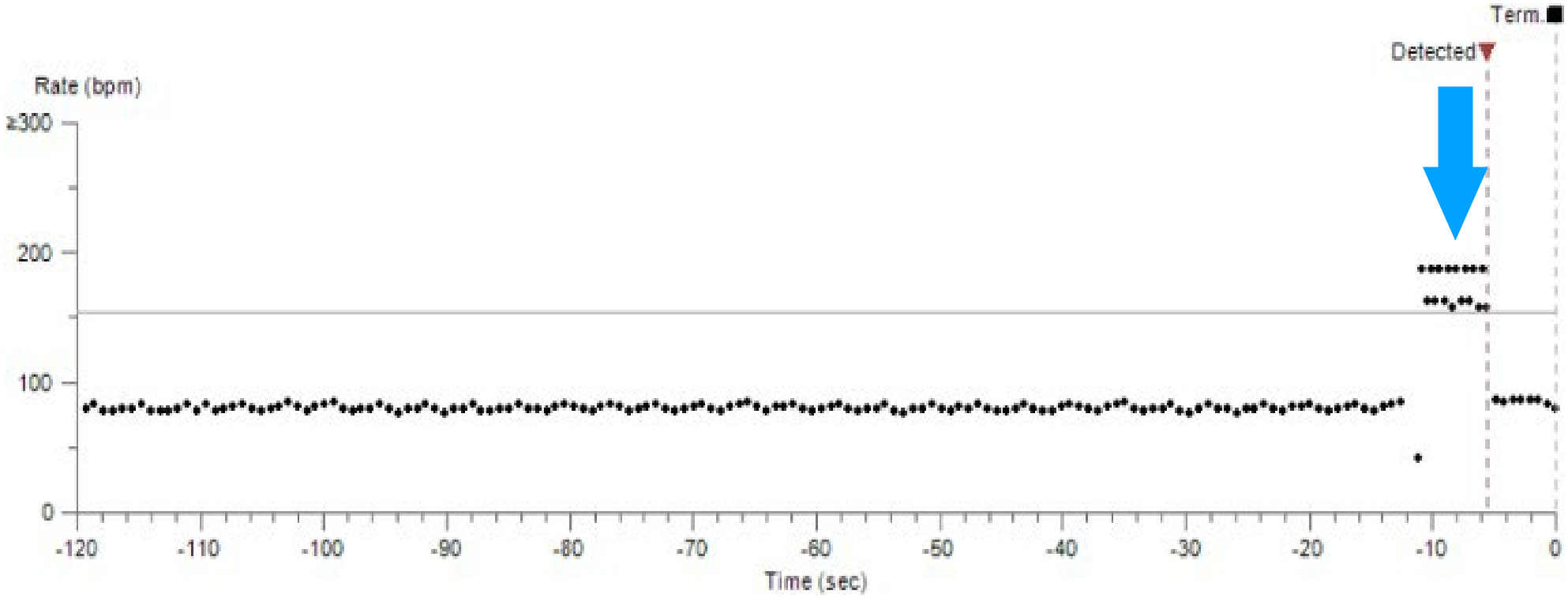
2 i


Term.
Detected
Rate (bpm)
≥300
200
100
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)

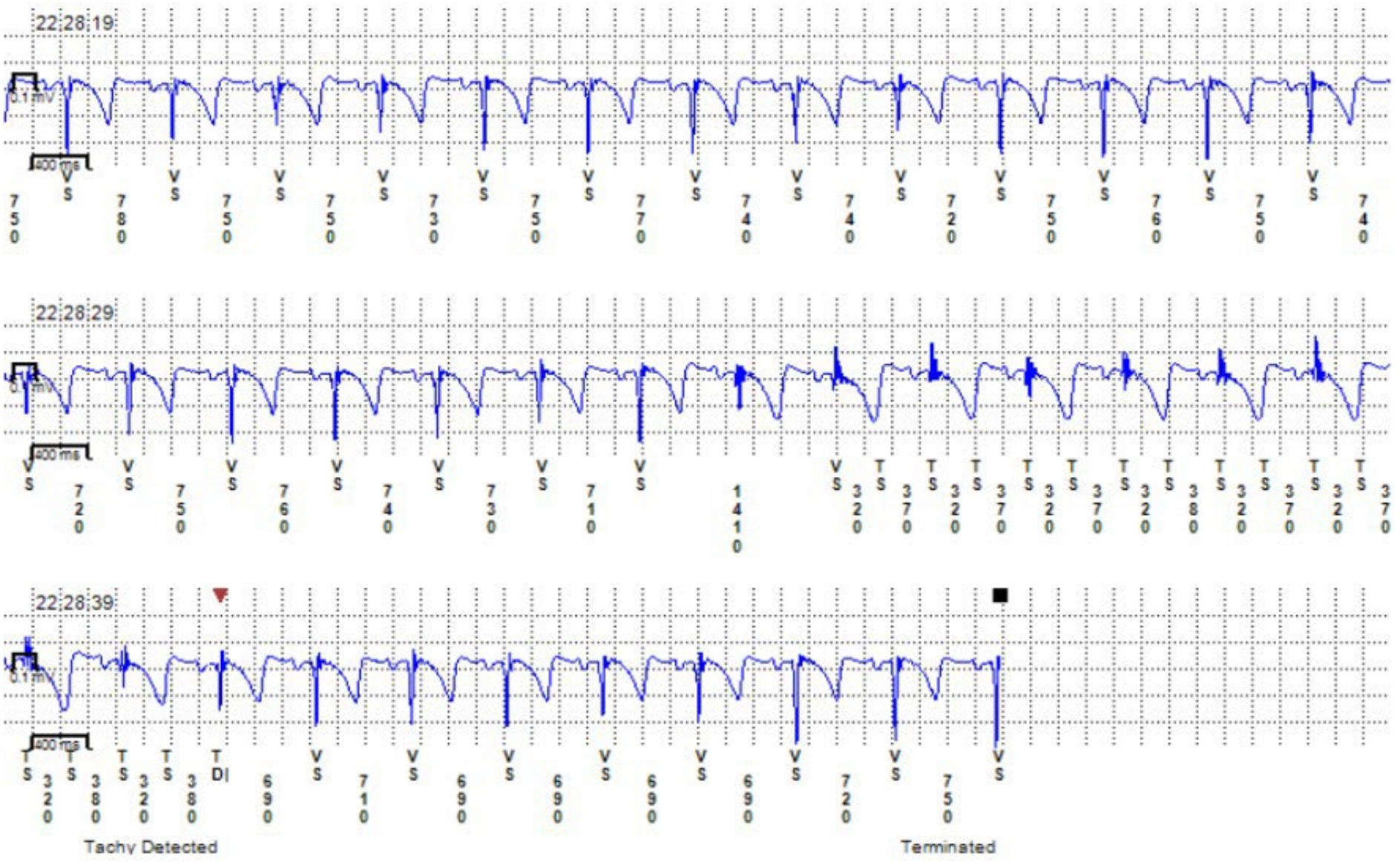
2 j


13:51:50
1 mV
400 ms
13:52:00
1 mV
400 ms
DI
hv Detected
Terminated
Tac

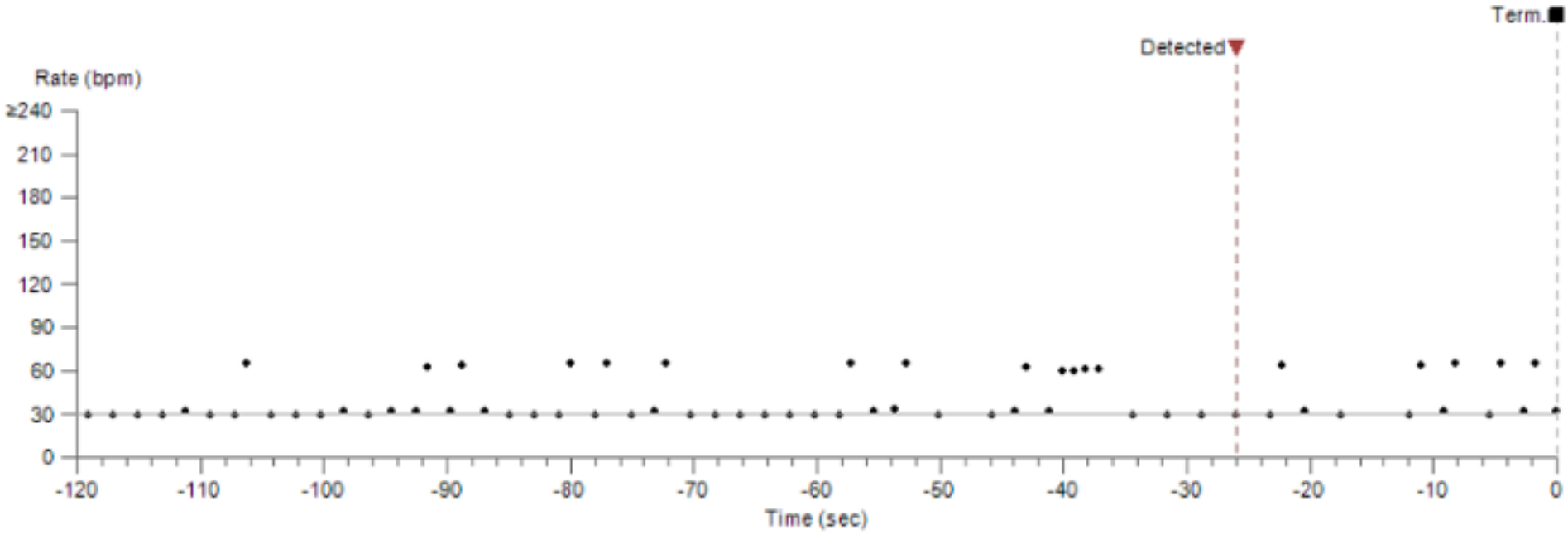
2 k


Term.
Detected
Rate (bpm)
≥300
200
100
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)

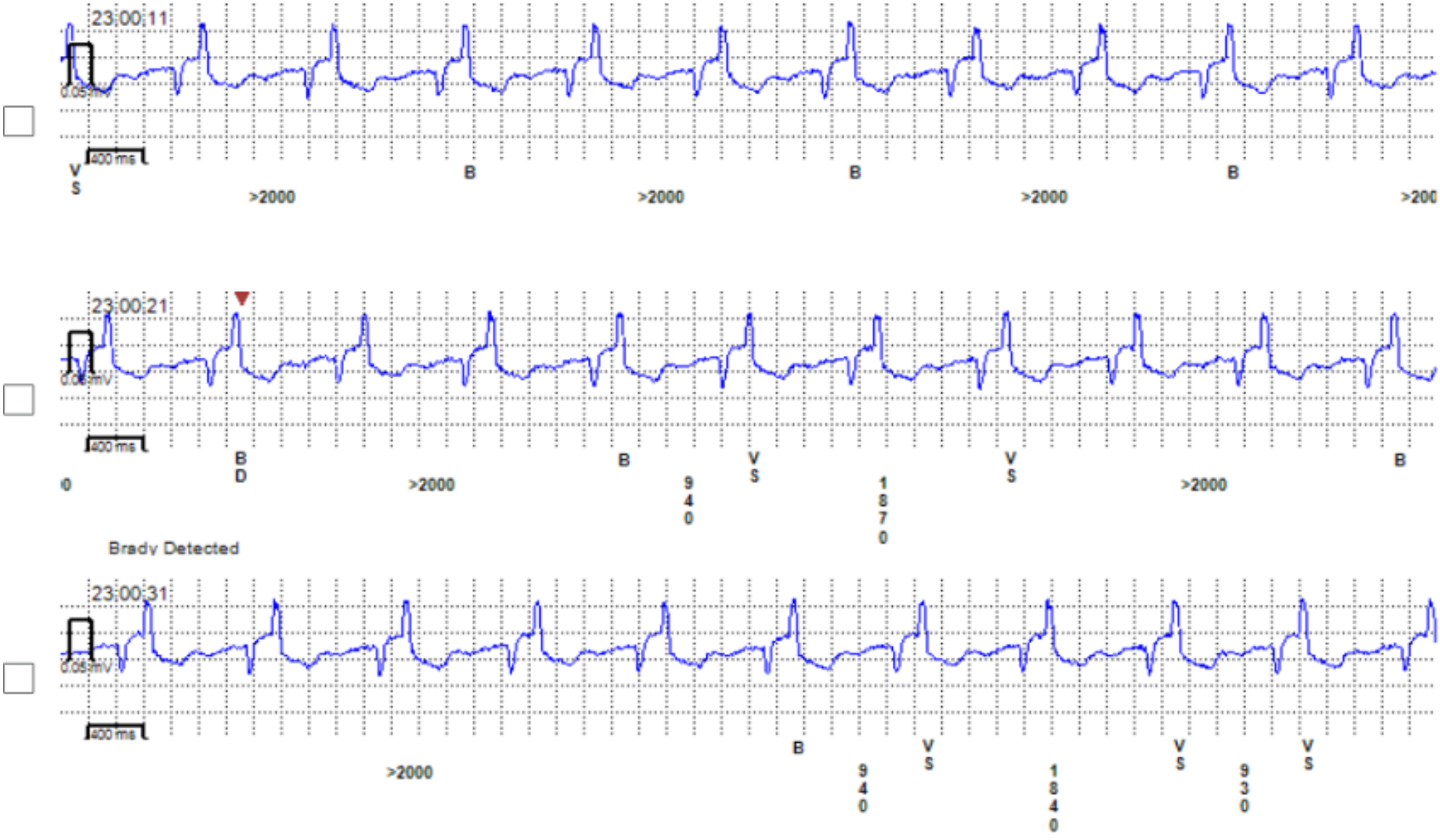
2 |


22:28:19
0.1 mV
400 ms
22:28:29
0.1 mV
400 ms
22:28:39
0.1 mV
400 ms
Tachy Detected
Terminated

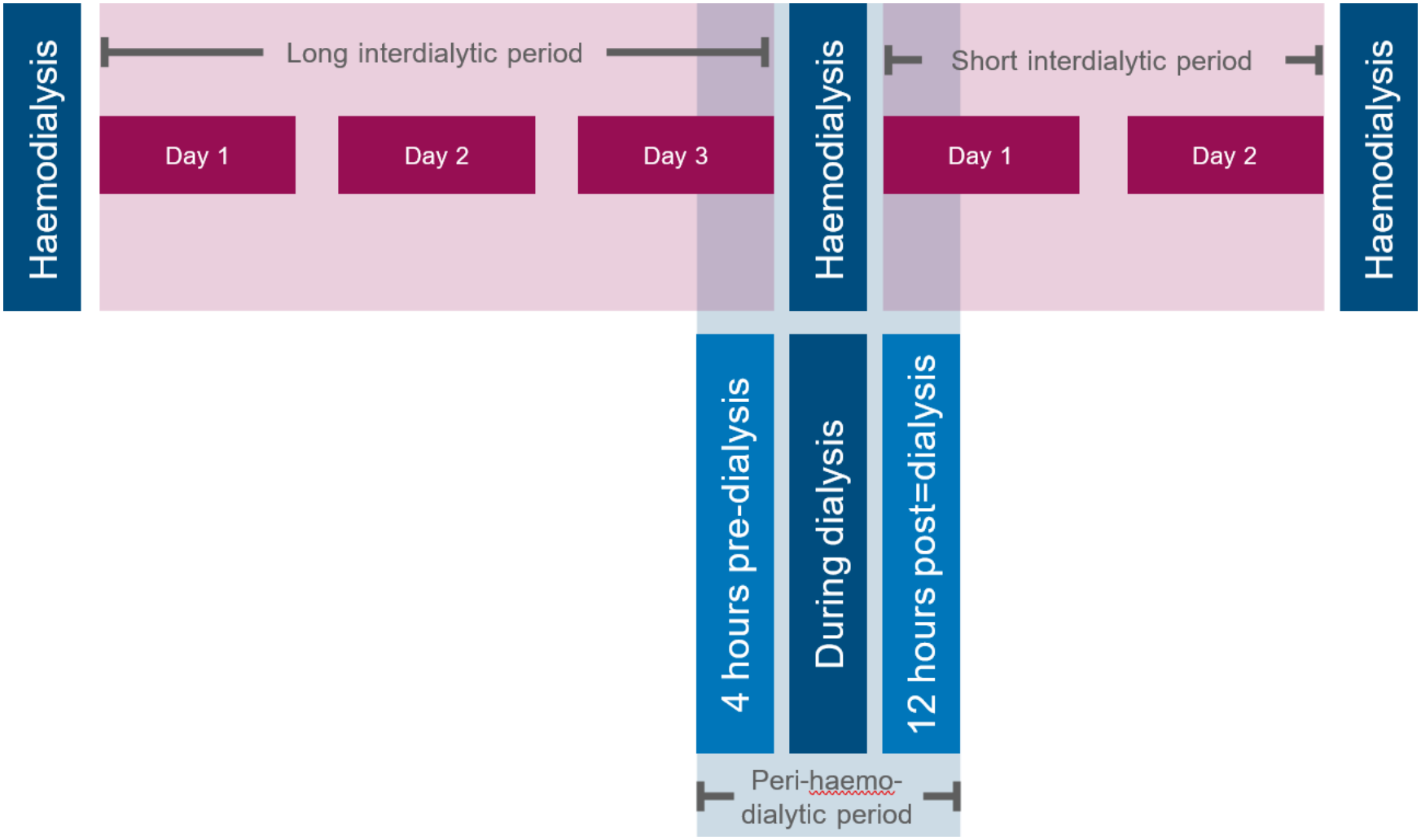
2 m


Term.
Detected
Rate (bpm)
≥240
210
180
150
120
90
60
30
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)

2 n


23:00:11
0.05 mV
400 ms
V
S
>2000
B
>2000
B
>2000
B
>200
23:00:21
0.05 mV
400 ms
0
B
D
>2000
B
9
4
0
V
S
1
8
7
0
V
S
>2000
B
Brady Detected
23:00:31
0.05 mV
400 ms
>2000
B
9
4
0
V
S
1
8
4
0
V
S
9
3
0
V
S

Supplemental Fig. 1 – schematic of dialysis timing definitions



List of Appendices

Appendix 1: Consent form

Division of Cardiology, Department of Medicine, University of Cape Town
Tel: +27 21 404 6136 Fax: +27 21 404 6070
Email: charle.viljoen@uct.ac.za / ashley.chin@uct.ac.za

Cardiac Arrhythmias in patients on the Renal Replacement Programme at Groote Schuur Hospital

You have been invited to take part in a research study. Before you decide whether you would like to take part in this study, it is important that you understand why this research is being done and what your participation will involve. Please take time to read this information sheet carefully and discuss it with friends, relatives and your doctor, if you wish. This information sheet will tell you what the purpose of the study is and what will happen when you take part. Please feel free to ask us to explain anything that is not clear to you or if you would like more information about this study.

Why is this study being done?
This research study would like to study which arrhythmias occur in patients who are on haemodialysis. An arrhythmia is an abnormality of the electrical conducting system of the heart. These abnormal heart rhythms can be causes of serious medical conditions including stroke and sudden death.

Why are you being asked to take part?
You were included in the EPIQ study and had a Reveal LINQ™ implantable cardiac device inserted for that study. As part of routine follow-up, the information from the devices was downloaded and reviewed to ensure that you did not have any dangerous arrhythmias whilst being dialysed or between dialysis sessions. We would like to use this information to study arrhythmias in patients on haemodialysis and after kidney transplantation.

What will happen if you decide to take part in the study?
If you give permission to be enrolled in this study, information will be collected about your age, gender, medical conditions, symptoms, findings on clinical examination by your treating doctor (e.g., blood pressure, heart rate), tests done whilst you are in hospital or attending the Cardiac Clinic (including the routine blood tests, ECG, echocardiogram) and Renal Clinic including your dialysis details (weight, how much fluid was removed during dialysis). This study will in no way affect your clinical management as the data collection will be purely observational.

What are the risks and discomforts of this study?
There are no risks or discomforts in taking part in this study. Taking part in this study will not cause any additional tests to be done or different treatment to the standard of care to be given.

Are there any benefits to you for being in this study?
There is no direct benefit to you to take part in this study. Your participation will help us to improve our understanding of arrhythmias in patients on haemodialysis and after transplant. This will help us gather information which may lead to improving care of patients with chronic kidney disease.

What other choices do you have?
There will be no repercussions if you decide not to take part in this study.

What will happen when the study is over?
We anticipate that the results of this study will be published in a medical journal for the benefit of the wider medical community. You will not be identified in any publication, because your personal and clinical details will remain strictly confidential.

Will the results of the research be shared with you?
Any scientific publications arising from the study will be available on your request.

Will any of your blood, tissue or other samples be stored and used for research in the future?
No, this study does not collect or store any blood, tissue or other samples other than the routine tests.

Will you receive any reward (money or food vouchers) for taking part in this study?
You will receive no reward (money or food parcel) for taking part in this study. You would also have no legal right to a share of any profits that may arise from this research.

How many people will take part in the study?
This study plans to include the 20 participants of the EPIQ study (HREC ref. no. 058 / 2015).

What is the study period under investigation?
The period under study will be the duration of the battery life of the Reveal LINQ™ implantable cardiac device, which is approximately from the 1st August 2015 until 31st July 2018.

Who will see the information which is collected about you during the study?
All information collected about you will be kept secure by the Cardiac Clinic Research Unit for a period specified by the South African Good Clinical Practice Guideline (SA GCP). All information will remain confidential and will only be available to the investigators of this study. All information will be made anonymous before it is studied and analysed.

Who could you contact about this study?
The contact details of the Cardiac Clinic Research Unit appear on the front page of this information sheet.

You could contact Dr Viljoen (charle.viljoen@uct.ac.za) or Professor Chin (ashley.chin@uct.ac.za) if you have any questions about this study in future.

If you have any ethical concerns about the "Cardiac Arrhythmias in patients on the Renal Replacement Programme at Groote Schuur Hospital" study, you may contact the Human Research Ethics Committee (HREC) at the Faculty of Health Sciences at the University of Cape Town. The contact person at the HREC is Prof. Marc Blockman at Room K45-43 Old Main Building, Groote Schuur Hospital, Observatory, 7925. His office telephone number is 021 406 6496 and email address is marc.blockman@uct.ac.za.

Division of Cardiology, Department of Medicine, University of Cape Town
Tel: +27 21 404 6136 Fax: +27 21 404 6070
Email: charle.viljoen@uct.ac.za / ashley.chin@uct.ac.za

Informed consent form:

I agree to participate in the "Cardiac Arrhythmias in patients on the Renal Replacement Programme at Groote Schuur Hospital" study. I have been informed by the study investigator of the rationale for the study and that it will not involve any new investigations or procedures.

I understand that my participation will in no way interfere with the standard of care of my condition. I give permission to the study investigators to gather all relevant information about tests done to investigate my condition. I give the study investigators permission to contact my attending doctor(s) to additional medical information regarding my condition. All results that are relevant to the investigation and management of my condition will be made available to my attending doctor(s) and myself.

I understand that my participation in this study is entirely voluntary. I am free to refuse to participate or withdraw from the study at any time, without any repercussions or jeopardizing my future care. All information gathered is and will remain strictly confidential, and will only be used for research relating to the study of "Cardiac Arrhythmias in patients on the Renal Replacement Programme at Groote Schuur Hospital". I will not be identified in any published report.

If I have any additional questions, I may contact the Cardiac Clinic Research Unit (CCRU), of which I have been given the contact details.

By signing this form, I agree to participate in the "Cardiac Arrhythmias in patients on the Renal Replacement Programme at Groote Schuur Hospital" study and I have been given a copy of this consent form.

Participant name	Participant signature	Date
Witness name	Witness signature	Date
Investigator name	Investigator signature	Date

Appendix 2: Case report forms (CRF) for data collection

Confidential

Patient details

Record ID	
Folder number	
Surname	
First name	
Date of birth	

Clinical details

Record ID	_____
Start date of dialysis	_____
Date of implant	_____
Renal cohort	◯ dialysis ◯ transplanted
If transplanted, when?	_____
Dry weight	_____
Comorbidities	☐ HIV ☐ HPT ☐ DM ☐ Hyperlipidaema ☐ Ischaemic heart disease ☐ Heart failure ☐ Stroke
NYHA	◯ I ◯ II ◯ III ◯ IV
Cause of CKD	☐ HPT ☐ DM ☐ SLE ☐ GN ☐ HIV ☐ Other
Vascular access	◯ Perm cath ◯ Fistula ◯ Graft

Medication	☐ Furosemide ☐ Enalapril ☐ Losartan ☐ Amlodipine ☐ Atenolol ☐ Carvedilol ☐ Minoxidil ☐ Doxazosin ☐ ART ☐ Insulin ☐ Vit D ☐ CaCO3 ☐ ESA ☐ Iron supplementation

ECG

Record ID	_____
Date of ECG	_____
QRS rate	_____
RR interval	_____
Rate	◯ Bradycardia ◯ Normal rate ◯ Tachycardia
Rhythm	◯ Sinus rhythm with regular RR interval ◯ Sinus arrhythmia ◯ Atrial fibrillation ◯ Atrial flutter
P wave morphology in II	◯ Normal ◯ Left atrial enlargement ◯ Right atrial enlargement ◯ Bilateral atrial enlargement
P wave morphology in V1	◯ Normal ◯ Left atrial enlargement ◯ Right atrial enlargement ◯ Bilateral atrial enlargement
PR interval in ms	_____
QRS width in ms	_____
QRS axis	_____
QRS axis deviation	◯ Normal ◯ Left axis deviation ◯ Right axis deviation ◯ Extreme axis deviation
Good RWP	◯ Yes ◯ No
LVH by Sokolow-Lyon	◯ Yes ◯ No
LBBB	◯ Yes ◯ No
RBBB	◯ Yes ◯ No

Pathological Q waves	◯ Yes ◯ No
T wave inversion	◯ Yes ◯ No
QT interval measured	_____
QTc by Bazett	_____
QTc by Fridericia	_____

Echo

Record ID	
Date of ECHO	
IVSd	
IVSs	
LVDd	
LVDs	
LVPWd	
LVPWs	
Echo LVH	◯ Yes ◯ No
LVEF	
FS	
LA diameter	
Left atrial enlargement	◯ Yes ◯ No
Left atrial volume	
Mitral e	
Deceleration time	
Mitral a	
E/A ratio	

Lateral E'	
Septal E'	
Average E/E'	
TR velocity	
Diastolic dysfunction	◯ None ◯ Grade 1 ◯ Grade 2 ◯ Grade 3

Laboratory

Record ID	
Date of blood taken	
Pre dialysis Na	
Pre dialysis K	
Pre dialysis Urea	
Pre dialysis Creat	
Post dialysis Na	
Post dialysis K	
Post dialysis Urea	
Post dialysis Creat	
Calcium	
Phosphate	
KT / V	
Urea reduction ratio	
Hb	

Loop recorder interrogation

Record ID	
Date of loop interrogation	
Symptoms	
Tachy	
Pause	
Brady	
AT	
AF	
Percentage of time in AF/AT	

Loop recorder interrogation reviewed

Record ID	_____
Date of loop interrogation review by physician	_____
Tachy reviewed by physician: number different than loop	◯ Yes ◯ No
If yes, why different?	☐ T wave oversensing ☐ T wave undersensing ☐ P wave oversensing ☐ PVC
Reviewed number of tachy	_____
Pause reviewed by physician: number different than loop	◯ Yes ◯ No
Reviewed number of pause	_____
Alternative diagnosis to pause	◯ None ◯ AV block ◯ Ventricular undersensing
Brady reviewed by physician: number different than loop	◯ Yes ◯ No
Reviewed number of brady	_____
AT reviewed by physician: number different than loop	◯ Yes ◯ No
Reviewed number of AT	_____
AF reviewed by physician: number different than loop	◯ Yes ◯ No
Reviewed number of AF	_____
If yes, why different?	◯ T wave oversensing ◯ T wave undersensing ◯ Irregular RR interval with undersensed P waves

Symptom

Record ID	_____
Symptom date and time	_____
Does symptom correlate with arrhythmia	◯ Yes ◯ No

Sinus node dysfunction

Record ID	
Episode number	
Time of episode	
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	
RR interval during episode (ms)	
Type of sinus node dysfunction	◯ Sinus arrest ◯ Sinus exit block
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	
Weight before previous dialysis	
Weight after previous dialysis	
Amount of fluid taken off at previous dialysis	
Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	

Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	
Diastolic BP after next dialysis	

AV block

Record ID	_____
Episode number	_____
Time of episode	_____
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	_____
RR interval during episode	_____
PP interval during episode	_____
Type of AV block	◯ Mobitz 1 ◯ Mobitz 2 ◯ 2:1 AV block ◯ 3:1 AV block ◯ 4:1 AV block ◯ Second degree unspecified ◯ Third degree AV block
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Sinus tachycardia

Record ID	_____
Episode number	_____
Time of episode	_____
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	_____
RR interval during episode	_____
P wave rate during episode	_____
Max rate	_____
Median rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdiaytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Atrial tachycardia

Record ID	_____
Episode number	_____
Time of episode	_____
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	_____
RR interval during episode	_____
P wave rate during episode	_____
Max rate	_____
Median rate	_____
Average rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic Period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____

Amount of fluid taken off at previous dialysis	
Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Atrial fibrillation

Record ID	_____
Episode number	_____
Was the episode AF?	◯ Yes ◯ No
Symptom during episode	◯ Yes ◯ No
Time of episode	_____
Duration of episode (seconds)	_____
Max rate	_____
Median rate	_____
Average rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic Period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Atrial flutter

Record ID	
Episode number	
Time of episode	
Was the episode atrial flutter?	◯ Yes ◯ No
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	
RR interval during episode	
Max rate	
Median rate	
Average rate	
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic Period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	
Weight before previous dialysis	
Weight after previous dialysis	

SVT

Record ID	
Episode number	
Time of episode	
Was the episode an SVT?	◯ Yes ◯ No
Comments	
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	
RR interval during episode	
Max rate	
Median rate	
Average rate	
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	
Weight before previous dialysis	

Amount of fluid taken off at previous dialysis	
Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Weight after previous dialysis	
Amount of fluid taken off at previous dialysis	
Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

PAC

Record ID	_____
Episode number	_____
Time of episode	_____
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	_____
PAC description	◯ Couplet ◯ Triplet
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____
Systolic BP before previous dialysis	_____
Diastolic BP before previous dialysis	_____
Systolic BP after previous dialysis	_____

Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

PVC

Record ID	_____
Episode number	_____
Time of episode	_____
Symptom during episode	◯ Yes ◯ No
Duration of episode (seconds)	_____
PVC description	◯ Couplet ◯ Triplet
Coupling interval	_____
Average rate surrounding PVC	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIPD ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____
Systolic BP before previous dialysis	_____

Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Sustained monomorphic VT

Record ID	_____
Episode number	_____
Symptom during episode	◯ Yes ◯ No
Time of episode	_____
Duration of episode (seconds)	_____
RR interval during episode	_____
Max rate	_____
Median rate	_____
Average rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of next dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Non-sustained monomorphic VT

Record ID	_____
Episode number	_____
Symptom during episode	◯ Yes ◯ No
Time of episode	_____
Duration of episode (seconds)	_____
RR interval during episode	_____
Max rate	_____
Median rate	_____
Average rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Non-sustained polymorphic VT

Record ID	_____
Episode number	_____
Symptom during episode	◯ Yes ◯ No
Time of episode	_____
Duration of episode (seconds)	_____
RR interval during episode	_____
Max rate	_____
Median rate	_____
Average rate	_____
Activity level	◯ Inactive ◯ Active
Relation to dialysis	◯ Not on dialysis ◯ Pre-dialysis ◯ During dialysis ◯ Post dialysis ◯ Between dialysis sessions
Interdialytic period	◯ SIDP ◯ LIDP ◯ During dialysis
Date of dialysis before event	_____
Weight before previous dialysis	_____
Weight after previous dialysis	_____
Amount of fluid taken off at previous dialysis	_____

Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Systolic BP before previous dialysis	
Diastolic BP before previous dialysis	
Systolic BP after previous dialysis	
Diastolic BP after previous dialysis	
Date of dialysis after event	
Weight before next dialysis	
Weight after next dialysis	
Amount of fluid taken off at next dialysis	
Systolic BP before next dialysis	
Diastolic BP before next dialysis	
Systolic BP after next dialysis	
Diastolic BP after next dialysis	

Appendix 3: Ethics Approval

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.3.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	2/3/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thk you for the dentin document/R

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	22/02/2022		
HREC REF Number	684/2019	Current Ethics Approval was granted until	30/10/2021
Protocol title	Cardiac Arrhythmias in Patients on the Renal Replacement Programme at Groote Schuur Hospital		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☒ No	
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Ashley Chin		
Department / Office Internal Mail Address	ashley.chin@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

INTERNATIONAL JOURNAL OF CARDIOLOGY

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 0167-5273

DESCRIPTION

The *International Journal of Cardiology* is devoted to cardiology in the broadest sense. Both basic research and clinical papers can be submitted. The journal serves the interest of both practicing clinicians and researchers.

In addition to original papers, we are launching a range of new manuscript types, including Consensus and Position Papers, Systematic Reviews, Meta-analyses, and Short communications. Case reports are no longer acceptable. Controversial techniques, issues on health policy and social medicine are discussed and serve as useful tools for encouraging debate.

International Journal of Cardiology has no page charges.

A reduced personal subscription rate is available; please apply to the Publisher for more information.

A reduced personal subscription rate is also available to all members of the International Society for Adult Congenital Heart Disease Please apply to the ISACHD for more information.

Personal and member subscribers can access the journal online via: http://www.internationaljournalofcardiology.com.

Institutional subscribers can access the journal online via ScienceDirect. For more information, please go to: http://www.sciencedirect.com.

AUDIENCE

Cardiologists, cardiac surgeons, pediatric cardiologists, researchers in cardiovascular diseases.

IMPACT FACTOR

2018: 3.471 © Clarivate Analytics Journal Citation Reports 2019

ABSTRACTING AND INDEXING

Embase
PubMed/Medline
Elsevier BIOBASE
Current Contents - Life Sciences
Index Internacional de Cardiologìa
SIIC Data Bases
BIOSIS Citation Index
Scopus
Science Citation Index
Science Citation Index Expanded
Current Contents - Clinical Medicine

EDITORIAL BOARD

Vanessa Ferreira, Oxford, United Kingdom
Gerasimos Filippatos, Athens, Greece
Nikolaos G. Frangogiannis, Bronx, United States
Ben Freedman, Concord, Australia Fiorenzo Gaita,
Torino, Italy Nazzareno Galié, Bologna, Italy
Stefano Ghio, Pavia, Italy
Simon Gibbs, London, United Kingdom Alessia
Gimelli, Pisa, Italy Massimiliano Gnecchi, Pavia, Italy
Bulent Gorenek, Eskisehir, Turkey Giulio Guagliumi,
Bergamo, Italy Marco Guazzi, Milano, Italy
Ya-Ling Han, Beijing, China Koji
Hasegawa, Kyoto, Japan Kristina Haugaa,
Oslo, Norway
Jordi Heijman, Maastricht, Netherlands
Gerd Heusch, Essen, Germany
Sang Hong Baek, Seoul, Korea, Republic of John Horowitz,
Woodville South, Australia Ciro Indolfi, Catanzaro, Italy
Jonathan Kalman, Parkville, Melbourne, Australia
Adnan Kastrati, Munchen, Germany Attila Kiss,
Vienna, Austria Masafumi Kitakaze, Suita, Japan
Petra Kleinbongard, Essen, Germany Karin
Klingel, Tuebingen, Germany
Paul Knaapen, Amsterdam, Netherlands Yoon Kwang Lee,
Rootstown, United States Giovanni La Canna, Milano, Italy
Patrizio Lancellotti, Liege, Belgium Ulf
Landmesser, Berlin, Germany Gaetano Lanza,
Milan, Italy Bernard Levy, Paris, France
Luca Liberale, Zürich, Switzerland
Giuseppe Limongelli, Napoli, Italy
Massimo Lombardi, San Donato Milanese, Italy Alberto
Lorenzatti, Cordoba, Argentina Matthew Huei-Ming Ma,
Taipei, Taiwan
Calum MacRae, Boston, United States Rosalinda
Madonna, Chieti, Italy Francesco Maisano, Zürich,
Switzerland Alberto Margonato, Milano, Italy
Mario Marzilli, Pisa, Italy
Pier Giorgio Masci, Lausanne, Switzerland
Patrizio Mazzone, Milano, Italy
Lorenzo Menicanti, San Donato Milanese, Italy Claudia Montanaro,
London, United Kingdom Fabrizio Montecucco, Genova, Italy
Toyoaki Murohara, Nagoya, Japan Kenichi
Nakajima, Kanazawa, Japan Sunao Nakamura,
Chiba, Japan Josè C. Nicolau, São Paulo, Brazil
Steven E. Nissen, Cleveland, United States Vahagn
Ohanyan, Rootstown, United States Iacopo Olivotto,
Firenze, Italy
Torbjorn Omland, Lørenskog, Norway
Milton Packer, Dallas, United States
Seung-Jung Park, Songpa-gu, Korea, Republic of
Guido Parodi, Firenze, Italy
Gerard Pasterkamp, Utrecht, Netherlands
Antonio Pelliccia, Roma, Italy Francesco Pelliccia,
Roma, Italy Pasquale Perrone-Filardi, Napoli, Italy
Piotr Ponikowski, Wroclaw, Poland Eva Prescott,
København, Denmark
Valentina Puntmann, Frankfurt am Main, Germany

Priya Raman, Rootstown, United States
K. Srinath Reddy, New Delhi, India Zeljko Reiner,
Zagreb, Croatia Leonardo Roever, UBERLANDIA,
Brazil Stuart Rosen, London, United Kingdom
Raphael Rosenhek, Wien, Austria Luís M. Ruilope,
Madrid, Spain
Nizal Sarrafzadegan, Isfahan, Iran, Islamic Republic of
Stefano Savonitto, Lecco, Italy
Thomas Schindler, Saint Louis, United States Heinz Peter
Schulteiss, Berlin, Germany Sebastiano Sciarretta, Rome,
Italy Susanna Sciomer, Roma, Italy
Udo Sechtem, Stuttgart, Germany
Joseph Selvanayagam, Bedford Park, Australia
Michele Senni, Bergamo, Italy Dipen Shah,
Geneva, Switzerland Hiroaki Shimokawa,
Sendai, Japan
Maria Siebes, Amsterdam, Netherlands Sigmund
Silber, München, Germany Gerald Simonneau,
Clamart, France Gianfranco Sinagra, Trieste, Italy
Karin Sipido, Leuven, Belgium
Karen Sliwa-Hahnle, Observatory, South Africa
Jasmeet Soar, Bristol, United Kingdom Paul Sorajja,
Minneapolis, United States Felix Tanner, Zürich,
Switzerland Michal Tendera, Katowice, Poland
Giuliano Tocci, Roma, Italy
Dimitris Tousoulis, Athens, Greece Johnathan Tune,
Indianapolis, United States Thomas Unger, Maastricht,
Netherlands Viola Vaccarino, Atlanta, United States
Tim Van De Hoef, Amsterdam, Netherlands Fiona Walker,
London, United Kingdom Stephan Windecker, Bern,
Switzerland Raymond L. Woosley, Oro Valley, United States
Joseph C. Wu, Stanford, United States
Mohammad Yaraghi, Isfahan, Iran, Islamic Republic of
Liya Yin, Rootstown, United States Jose Luis
Zamorano, Madrid, Spain Dong Zhao, Beijing,
China

GUIDE FOR AUTHORS

Introduction

The International Journal of Cardiology is a global journal of cardiology, cardio-metabolic and vascular sciences. Articles reporting clinical observations and interventions, experimental studies and theoretical concepts are all welcome provided they are of major scientific importance and clinical relevance. The journal covers all aspects of cardiology from genes to populations. The journal commissions high quality review articles from distinguished authors. Submission of a manuscript to this journal gives the publisher the right to publish that paper if it is accepted. Manuscripts may be edited to improve clarity and expression

INTRODUCTION

The International Journal of Cardiology is a global journal of cardiology that welcomes the following types of articles:

Original articles

Text in these articles should not exceed **3,500** words, **50** references and **4** tables/figures. Additional references and/or methods will be published online only.

This category includes the following types of articles:

Original clinical research studies, basic science/translational research papers: International Journal of Cardiology publishes articles highlighting all aspects of cardiovascular disease, including original clinical studies in the fields of clinical investigation, pharmacotherapy, genetics, cardiovascular imaging, intervention, structural heart disease, etc.- clinical trials, meta-analyses, pathophysiological investigations, experimental studies with clinical relevance and state-of-the-art papers. Cardiovascular basic science research studies with a strong clinical translational component will be considered for publication. Basic science papers usually depict research carried out in experimental animals, cells, or tissue. The abstract section of these papers should include a paragraph or two (**50-75** words) describing the translational aspect of the work.

Consensus and Position Papers
Usually produced by recognized institutions or working groups these articles provide expert opinion on topical issues in cardiovascular medicine and related disciplines which are of high interest and potential value for the practicing cardiologist as well as regulatory agencies, national and international societies and Society in general. These articles generally deal with issues that are not specifically covered by current international guidelines and therefore constitute unmet needs.

Systematic reviews and meta-analyses
These manuscripts are systematic assessments of the evidence available in the medical literature regarding specific issues, including pathophysiological mechanisms, diagnosis, prognosis, disease treatment, preventative management, etc. An established methodology exists for the production of these articles. For advice on systematic review preparation consult the Cochrane Reviewers' Handbook.

Short communication
Short communication should contain original data as per the description given under "original articles" but their length should not exceed **1,500** words; **20** references; **2** figures/tables. Case reports are not acceptable under this category.

This manuscript category may include clinical studies/high quality observational work - either clinical or experimental - reflecting novel preliminary findings or results of studies that can be summarised in under 1500 words. These articles may be hypothesis generating and/or able to stimulate research in a specific area. A structured abstract (around 200 words) is required and the article should be structured in the same fashion as original papers. Illustrative figures are welcome.

Editorials
Editorial articles are commissioned by the Editor-in-Chief and aim to provide brief expert views on specific manuscripts published in a given IJC issue. These articles should contain a max. of **1,000** words; **10** references; **1** figure/table

Letters to the Editor
The content of a letter to the Editor must **relate** to a **specific article** published in IJC; max **250** words; **5** references; **no** figures/tables. We only accept Letters to the Editor that challenge previously published articles in the *International Journal of Cardiology* by raising specific questions and/or concerns that authors of the referenced paper can be invited to address.
No more of three Letters to the Editor from the same author(s) can be published in our Journal in one year. IJC only accepts Letters to the Editor that challenge previously published articles in the International Journal of Cardiology by raising specific questions and/or concerns that authors of the referenced paper can be invited to address

PREPARATION OF MANUSCRIPTS:

Original articles and Short communication should be structured as following:

Divide the manuscript into the following sections: Title page, Structured Abstract, Key words (3-6), Introduction, Methods, Results, Discussion, Acknowledgments, References. The editors will consider the use of other sections if more suitable for certain manuscripts. Type double-spaced. The Title Page should include: 1. The title (not to exceed 25 words) 2. The full list of authors and for each author a numbered footnote. The footnote should state the author's academic affiliation and the following statement of authorship: "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation". Any author unable to make this statement must instead state their specific contribution to the manuscript. 3. Corresponding author and contact details 4. Acknowledgement of grant support 5. Any potential conflicts of interest, including related consultancies, shareholdings and funding grants 6. A list of up to 6 keywords The Next Page Should Include:

A Structured Abstract, of no more than 250 words. As this may be the only part of the article read by some readers it must include sufficient detail for an adequate summary of the whole manuscript. The preferred subheadings are Background, Methods, Results and Conclusions, although a merged Methods and Results subheading is also permitted if this permits more economical expression. The Next Page should commence the main article subdivided into the following sections:

The Introduction should be brief and set out why the study has been performed along with a review of relevant previous work only where essential.

The Methods should be sufficiently detailed so that readers and reviewers can understand precisely what has been done. Standard methods can be referenced. Manuscripts reporting data obtained from research conducted in human subjects must include a statement of assurance in the Methods section of the manuscript that (1) informed consent was obtained from each patient and (2) the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval

by the institution's human research committee. Manuscripts reporting experiments using animals must include a statement giving assurance that all animals received humane care and that study protocols comply with the institution's guidelines.

A Statistical Methods Section must be included where relevant. This should include the statistical methods used with sufficient clarity for the findings to be reproduced by independent analysis of the dataset, a statement on how the data presented were selected including prospective sample size calculations, the reasons for including/excluding subjects or data points, and what steps the authors have taken, if any, to exclude intentional or unintentional bias in recruitment, measurement, data retention, analysis, reporting and comment.

The Results should be presented precisely. Keep discussion of their importance to a minimum in this section of the manuscript. Present 95% confidence intervals with p values. When describing normal distributions, denote the standard deviation explicitly, e.g. with the abbreviation SD, rather than a sign. When describing uncertainty of a mean, denote the standard error of the mean explicitly, e.g. with the abbreviation SEM, rather than a sign. It is a condition of final acceptance of manuscripts, for the purpose of scientific integrity, that for each figure, raw numerical values should be uploaded in an Online Data Supplement. These supplement files should be one or more standard spreadsheet files. Raw x and y values for all scatterplots should be given. For bar charts and histograms, underlying raw values and categories should be given. For each Kaplan-Meier survival curve, for each patient a time-to-event-or-censoring and censor status should be given. Authors may additionally optionally upload comprehensive numerical datasets of the study.

The Discussion should directly relate to the study being reported rather than a general review of the topic.

A Study limitations subsection must be included and should disclose any reasons the findings may not be applicable more broadly.

Conclusions should be limited to a brief summary and the implications of the data presented.

References Discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links within ScienceDirect and to abstracting and indexing services, such as Scopus, CrossRef or PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent the link creation. When copying references, please be careful as they may already contain an error.

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume and issue/book chapter and the pagination must be present. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that incorrect or missing data will be highlighted at proof stage for the author to correct.The reference style used by this journal is Vancouver Numbered. If you do wish to format the references yourself they should be arranged according to the following examples Examples: [1] De Soyza N, Thenabadu PN, Murphy ML, Kane JJ, Doherty JE. Ventricular arrhythmia before and after aortocoronary bypass surgery. Int J Cardiol 1981; 1:123-130. [2] Akutsu T. Artificial heart: total replacement and partial support. Amsterdam: Elsevier/North-Holland, 1975. [3] Goldman RH. Digitalis toxicity. In: Bristow MR, editors. Drug-induced heart disease. Amsterdam: Elsevier/North- Holland, 1980:217-40.

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either "in preparation" or "submitted for publication". If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against reference list after your manuscript has been revised.

Tables should be typed with double spacing and each should be on a separate sheet. They should be numbered consecutively with Arabic numerals, and contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanations underneath. Figures should ideally be submitted in high-resolution TIF format, or alternatively in GIF, JPEG/JPG, or EPS format. The figures should be placed in separate files, named only with the figure numbers (e.g. "Figure1.tif".) The cost of colour figures will be paid by the author.

Please ensure figures have the appropriate resolution: Line art: 1000 dpi Halftones: 300 dpi Combinations: 500 dpi Colour: 300 dpi Colour combinations: 500 dpi.

Figures can appear in colour in the online journal at no additional cost to the author, but if the author requires the paper journal to show the figures in colour there is an additional cost to pay.

For further information on the preparation of electronic artwork, please seehttp:// authors.elsevier.com/artwork. Legends for Figures should be typed with double-spacing on a separate sheet.

For each and every gene accession number cited in an article, authors should type the accession number in bold, underlined text. Letters in the accession number should always be capitalised. Example: (GenBank accession nos. AI631510, AI631511, AI632198, and BF223228,) a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. BE675048,) and a T-cell lymphoma (GenBank accession no. AA361117).

Process of Submission

The International Journal of Cardiology is a fully electronic journal. All manuscripts MUST be submitted via the Internet to the following Elsevier website: https://www.evise.com/profile/api/navigate/IJC. DO NOT email the manuscript to the journal or editors.

Author Agreement Form All authors and contributors must submit a form stating their role in the article. This form is available to download directly from the last screen in the submission process. The International Journal of Cardiology requires all authors to sign this form. Articles will not be published until these are received.

Changes to Authorship This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts: Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written signed confirmation from ALL authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above.

Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed. After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article already published online must follow the same policies as noted above. If accepted, the change will be noted by the publication of a corrigendum.

Preparation of supplementary data International Journal of Cardiology publishes electronic supplementary material to enhance your scientific research presentation, increase transparency, and support scientific integrity. It is required that raw data for figures should be presented, and the author is invited voluntarily to publish in full the detailed dataset of the study. Supplementary files may also include supporting applications, movies, animation sequences, high-resolution images, background datasets, sound clips or other helpful items. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier web products, including ScienceDirect: http://www.sciencedirect.com.
Language Editing The language of the Journal is English. International Science Editing and Asia Science Editing can provide English language and copyediting services to authors who want to publish in scientific, technical and medical journals and need assistance before they submit their article or, before it is accepted for publication. Authors can contact these services directly: International Science Editing (http://www.internationalscienceediting.com) and Asia Science Editing (http://www.asiascienceediting.com) or, for more information about language editing services, please visit our Support Center.

Page charges

Page Charges will not be levied.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
E-mail address
Full postal address

All necessary files have been uploaded:
Manuscript:
Include keywords
All figures (include relevant captions)
All tables (including titles, description, footnotes)
Ensure all figure and table citations in the text match the files provided
Indicate clearly if color should be used for any figures in print *Graphical Abstracts / Highlights files* (where applicable) *Supplemental files* (where applicable)

Further considerations
Manuscript has been 'spell checked' and 'grammar checked'
All references mentioned in the Reference List are cited in the text, and vice versa
Permission has been obtained for use of copyrighted material from other sources (including the Internet)
A competing interests statement is provided, even if the authors have no competing interests to declare
Journal policies detailed in this guide have been reviewed
Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the

Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places:
1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted.
2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Conflict of interest statements for authors

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. See also https://www.elsevier.com/conflictsofinterest.

The International Journal of Cardiology requires full disclosure of all potential conflicts of interest. Please download the disclosure from the submission site, at the 'Attach Files' stage of manuscript submission

Potential Conflicts of Interest Related to Individual Authors' Commitments When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist.

Further information and an example of a Conflict of Interest form can be found at:
http://service.elsevier.com/app/answers/detail/a_id/286/supporthub/publishing

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright- holder. To verify originality, your article may be checked by the originality detection service Crossref Similarity Check.

Preprints

Please note that preprints can be shared anywhere at any time, in line with Elsevier's sharing policy. Sharing your preprints e.g. on a preprint server will not count as prior publication (see 'Multiple, redundant or concurrent publication' for more information).

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Articles should make no assumptions about the beliefs or commitments of any reader, should contain nothing which might imply that one individual is superior to another on the grounds of race, sex, culture or any other characteristic, and should use inclusive language throughout. Authors should ensure that writing is free from bias, for instance by using 'he or she', 'his/her' instead of 'he' or 'his', and by making use of job titles that are free of stereotyping (e.g. 'chairperson' instead of 'chairman' and 'flight attendant' instead of 'stewardess').

Author contributions

For transparency, we encourage authors to submit an author statement file outlining their individual contributions to the paper using the relevant CRediT roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Authorship statements should be formatted with the names of authors first and CRediT role(s) following. More details and an example

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.

Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Clinical trial results

In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

Reporting clinical trials

Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram are available online.

Registration of clinical trials

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors recommendations. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or

participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal. More information.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

For gold open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (more information). Permitted third party reuse of gold open access articles is determined by the author's choice of user license.

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing

Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies

Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the gold open access publication fee. Details of existing agreements are available online.

After acceptance, open access papers will be published under a noncommercial license. For authors requiring a commercial CC BY license, you can apply after your manuscript is accepted for publication. *Open access*

This journal offers authors a choice in publishing their research:

Subscription

Articles are made available to subscribers as well as developing countries and patient groups through our universal access programs.

No open access publication fee payable by authors.

The Author is entitled to post the accepted manuscript in their institution's repository and make this public after an embargo period (known as green Open Access). The published journal article cannot be shared publicly, for example on ResearchGate or Academia.edu, to ensure the sustainability of peer- reviewed research in journal publications. The embargo period for this journal can be found below. *Gold open access*

Articles are freely available to both subscribers and the wider public with permitted reuse.

A gold open access publication fee is payable by authors or on their behalf, e.g. by their research funder or institution.

Regardless of how you choose to publish your article, the journal will apply the same peer review criteria and acceptance standards.

For gold open access articles, permitted third party (re)use is defined by the following Creative Commons user licenses:

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

The gold open access publication fee for this journal is **USD 3650**, excluding taxes. Learn more about Elsevier's pricing policy: https://www.elsevier.com/openaccesspricing.

Green open access

Authors can share their research in a variety of different ways and Elsevier has a number of green open access options available. We recommend authors see our open access page for further information. Authors can also self-archive their manuscripts immediately and enable public access from their institution's repository after an embargo period. This is the version that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and in editor-author communications. Embargo period: For subscription articles, an appropriate amount of time is needed for journals to deliver value to subscribing customers before an article becomes freely available to the public. This is the embargo period and it begins from the date the article is formally published online in its final and fully citable form. Find out more.

This journal has an embargo period of 12 months.

Elsevier Researcher Academy

Researcher Academy is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's Author Services.

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author but copies should not be provided to the journal. Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer- review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article

Please submit your article via https://www.evise.com/profile/api/navigate/IJC.

Referees

Please submit the names and institutional e-mail addresses of several potential referees. For more details, visit our Support site. Note that the editor retains the sole right to decide whether or not the suggested reviewers are used.

PREPARATION

Peer review

This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation

A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower- case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post- publication. This responsibility includes answering any future queries about Methodology and Materials. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.
Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights

Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.
Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Submission of Genetic Information

Every gene, DNA sequence, cell line and polymorphism/variant referred to in an article must adhere to standardized nomenclature as outlined below:

Only gene names approved by the HUGO Gene Nomenclature Committee should be used: http://www.genenames.org All DNA sequences and GenBank accession.version numbers must be included in the text of the article. Example: (GenBank: AI631510.1, GenBank: AI631511.1, GenBank: AI632198.1, and GenBank: BF223228.1), a B-cell tumour from a chronic lymphatic leukaemia (GenBank: BE675048.1), and a T-cell lymphoma (GenBank: AA361117.1). The rs number must be provided for all SNPs/variants where available incl. a description of each variant using genomic coordinates. Example: rs28942083 NC_000019.10:g.11120382G>A http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=28942083 To describe sequence variants (DNA, RNA & protein), authors should use the recommendations of the HGVS: http://www.hgvs.org/mutnomen/. Tools such as the Mutalyzer software maybe used to assist with this www.mutalyzer.nl All data on genes, variants and phenotypes should be deposited in a public

repository: large rearrangements (CNVs), incl. dbVar, Decipher or LOVD gene variant databases, incl. ClinVar and LOVD (databases.http://www.lovd.nl/shared/). Available gene variant database can be identified using the url "GeneSymbol".LOVD.nl (e.g. TP53.LOVD.nl). In order to allow for the work to be reproduced by others, where not previously published, authors are encouraged to provide as supplementary material for web-publication only, the primers and PCR conditions for all variants genotyped in the manuscript.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Artwork *Electronic artwork General points*

Make sure you use uniform lettering and sizing of your original artwork.

Embed the used fonts if the application provides that option.

Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.

Number the illustrations according to their sequence in the text.
Use a logical naming convention for your artwork files.
Provide captions to illustrations separately.
Size the illustrations close to the desired dimensions of the published version.
Submit each illustration as a separate file.
Ensure that color images are accessible to all, including those with impaired color vision. A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.
Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi. TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
Supply files that are too low in resolution;
Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Illustration services

Elsevier's Author Services offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software

Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley. Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes from different reference management software.

Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/international-journal-of-cardiology

When preparing your manuscript, you will then be able to select this style using the Mendeley plug- ins for Microsoft Word or LibreOffice.

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.

Example: '..... as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result '

List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, J. Sci. Commun. 163 (2010) 51–59. https://doi.org/10.1016/j.Sc.2010.00372.

Reference to a journal publication with an article number:

J. van der Geer, J.A.J. Hanraads, R.A. Lupton, 2018. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon 2018.e00205.

Reference to a book:

W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.

Reference to a chapter in an edited book:
G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304. Reference to a website:
Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).
Reference to a dataset:
[dataset] [6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. https://doi.org/10.17632/ xwj98nb39r.1.

Journal abbreviations source

Journal names should be abbreviated according to the List of Title Word Abbreviations.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. . In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Data visualization

Include interactive data visualizations in your publication and let your readers interact and engage more closely with your research. Follow the instructions here to find out about available data visualization options and how to include them with your article.

Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Data linking

If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the database linking page.

For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Mendeley Data

This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

Data in Brief

You have the option of converting any or all parts of your supplementary or additional raw data into one or multiple data articles, a new kind of article that houses and describes your data. Data articles ensure that your data is actively reviewed, curated, formatted, indexed, given a DOI and publicly available to all upon publication. You are encouraged to submit your article for *Data in Brief* as an additional item directly alongside the revised version of your manuscript. If your research article is accepted, your data article will automatically be transferred over to *Data in Brief* where it will be editorially reviewed and published in the open access data journal, *Data in Brief*. Please note an open access fee of 600 USD is payable for publication in *Data in Brief*. Full details can be found on the Data in Brief website. Please use this template to write your Data in Brief.

Data statement

To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

AFTER ACCEPTANCE

Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the publisher within 2 days of receipt.

Online proof correction

Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.

If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.

We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints

The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra

charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Author Services. Corresponding authors who have published their article gold open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also check the status of your submitted article or find out when your accepted article will be published.