

Peer Review File

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Reviewer A

Comment: Thank you for submitting the manuscript regarding this important topic. Please note that there are significant number of grammar and formatting issues though out the manuscript which need to be addressed before this can be published.

Reply: The manuscript has been reviewed and corrected by a native speaker.

Changes in the text: The entire text underwent linguistic revisions.

Reviewer B

Comment: This is an interesting opportunity to leverage the venography done in relationship to CIED procedures to evaluate the patency of the central veins that would potentially be useful for placement of a port. The major point is that it is possible to have occlusion of the ipsilateral and contralateral side of pacemaker leads. Many of these venograms were done during a procedure to treat CIED infection, a pro inflammatory condition that increases the risk of stenosis/clot/occlusion.

Reply: Yes, CIED-related infections increases the risk of venous obstruction. It seems to be an example of a defence mechanism by which the flow of pus into the circulatory system is blocked. Our observations indicate that this is a permanent and even progressive phenomenon, which is not reversed by lead removal

Changes in the text: We added some data on page 10 lines 197-202.

Comment: This is not a systematic look at the contralateral system as it was viewed only when there was occlusion of the same side system. Therefore the numbers are not accurate, but are directional.

Reply: Yes, in some patients who have no collateral circulation, the assessment is an estimate, but in patients who have not previously had leads, ports, dialysis catheters removed on this side of the chest (which we know), the risk of underestimation error (which exists) is small.

Changes in the text: Comment on page 6, lines 109-113 was added.

Comment: I am most concerned about using the central veins for other reasons in the settings of CIED devices. This becomes a setup for infection, is this the reason for the 20% infections?

Reply: Our experience and observations confirm that chronic infection of CIED pocket may favour the development of venous occlusion. We have no data on the opposite

relationship. i.e. whether obstruction favours infection. Of course, the clotting factor is important in the formation of vegetations on the infected leads. Infected thrombosis in large veins, equivalent at some stage to the vegetations seen in the heart, is possible, but little is known about its evolution. Perhaps future studies using [18F] PET/CT and SPECT/CT will expand our understanding of the relationship between occlusion and thrombosis and infection.

Changes in the text: The same comment on page 10 lines 197-202.

Particularly dialysis catheters in the setting of pacemakers or ICDs greatly increase the risk of infection. What is more, when there is placement of dialysis catheters, on the same side as pacemaker/CIED leads, blood flow is poor and there is temptation to stent the vein open and trap the CIED lead systems. The caveats of stenosis and the problems of using the other catheters with CIED systems need to be emphasized.

Reply: Limitations of dialysis therapy in patients with CIEDs have been described in our previous report [Czajkowski M, Polewczyk A, Jacheć W, Nowosielecka D, Tułeckı Ł, Stefańczyk P, Kutarski A. How does a CIED presence influence chances and safety of haemodialysis access? Conclusions from over 3000 thoracic venographies. Clin Physiol Funct Imaging. 2023;43:47-57].

Changes in the text: Citation of the mentioned publication was added on page 4, line 74 and references number 11.

Comment: There are many venograms, but it needs to be clarified how often ipsilateral and contralateral stenosis was tested since usually just the ipsilateral side is evaluated. The contralateral side stenosis is likely underestimated.

Reply: Yes, we acknowledge, and it is noted in the manuscript and additionally in the Study Limitations section that there is a slight possibility of underestimation of venous stenoses on the side of the chest where contrast is not administered to a peripheral vein. We have concluded that the administration of an additional volume of contrast agent without a valid medical indication is not justified.

Changes in the text: Comments on page 6 lines 109-113 and on page 15 lines 311-314.

Reviewer C

This is a retrospective observational analysis of a large multi-center cohort of 3075 patients' venograms performed routinely before transvenous lead extraction (TLE) of cardiac implantable electronic devices (CIED) between 2008 and 2021. The study aimed to evaluate the rate of major thoracic vein obstruction (partial or total) in CIED carriers and the possible impact of vein thrombosis on central venous access device (CVAD) implantation. The manuscript is overall well written and does not require English language revision.

Comment 1 The title does not describe the true study design and could mislead the possibly interested reader. According to the study design, the cohort examined is comprised of patients undergoing TLE, not patients requiring central venous access.

Reply: The title has been modified

Changes in the text: Title

Comment 2 The abstract sums up the main contents of the work with coherence, however, the primary endpoint of the study is not mentioned (and should be mentioned).

Reply: One sentence summarizing the possibilities of effective introduction of the port and its proper functioning has been added to the Abstract and description of Table 2.

Changes in the text: Sentence in the abstract page 2-3, lines 46-50 and in the Table 2

Comment 3: The methods section clearly describe the study design and an extensive definition of vein occlusion degree is available. However, also in the methods section the primary endpoint of the study is not clarified and should be discussed in a separate sub-heading.

Reply: A large paragraph has been added in which methods of evaluation of the chance of inserting the port and its proper function are specified

Changes in the text: Comment on page 6 and 7 in lines 114-129

Other major issues:

Comment 4 Table 2: the meaning of this table is unclear. Instead of “rating of big chest vein” do the author mean “number of patients”? If yes, please clarify.

Reply: Table 2 seems to be the most important table in the article from a practical point of view and it is a response to the objectives of the study, which was to assess the chances of inserting venous ports in patients with CIEDs. The table shows the real possibilities of introducing the port (its passage up to the right atrium), taking into account the degree of patency of the veins along the route of the future port. In the Methods section, the methodology for assessing the chances of introducing the port and its proper function has been added.

Changes in the text: Comment on page 6 and 7 in lines 114-129.

Comment 5 The statistical analysis performed using Chi-square test is misleading and may be unrelated to the endpoint of the study. Indeed, a significant p value in this table would suggest a statistically significant difference between rate of possible CVAD implantation that may be considered more feasible on the opposite side of CIED.

Reply: The table is illustrative and practical rather than scientific. The differences in the percentages are very large and the conclusions from the table are obvious, even without statistical evaluation. Of course, venous patency is incomparable if we compare chest sides with and without leads. However, the message of this table was that the picture of venous patency is not binary and venous patency is not entirely predictable. The conclusion is that venography is a useful diagnostic method in patients with CIEDs who are planned for venous port implantation. Because even effective insertion of the port in the case of stenosed vein can close it completely.

Statistical comparison was conducted in order to unambiguously document the differences in the topography of stenoses, indeed the use of the classic Chi2 test may raise some objections. Therefore, the distribution of variables was comprehensively reassessed with the Pearson Chi2 test. The content of the "Statistics" subsection has been corrected.

Changes in the text: Comment on page 7, lines 136-140.

Comment 6 According to these results, the main conclusion of the study should be that there is higher success rate of CVAD implantation on the CIED-free side compared to the lead-side (indeed, only a small percentage of patients – 2.41% - carried abandoned leads on the opposite CIED side). These results seem to get in contrast with the conclusions of the authors (Line 240:” Venography seems to be valuable also if the utility of the opposite to the lead chest side is planned). Indeed, looking at the really small percentage of patients with abandoned leads opposite to the CIED location or with severe obstruction on the lead-free side (2%) the role of venography (that requires contrast administration and possible acute kidney injury in a frail patient cohort with a high rate of chronic kidney disease – 19%) is questionable and, in my opinion, may be avoided. Please comment and rebut.

Reply: No one (as a patient requiring a venous port) would like to be in this 2% group. The problem of port implantation in patients with even moderate obstruction also lies in collateral circulation and the danger of serious complications if the guidewire and introducer set enter the collateral circulation. We tried to present this issue (traps generated by collateral circulation) as well as the limitations of echographic assessment of local venous patency in the figures. In addition, there is the previously mentioned possibility of blocking the flow next to the port at the site of the narrowing of the vein.

Changes in the text: This is only the explanation to the Reviewer

Comment 7: If possible, to retrospectively retrieve these data, it would be interesting to know how many patients truly underwent CVAD (not only port-a-cath) implantation to understand the possible impact of the several degrees of major chest vein obstruction.

Reply: Unfortunately, this is not realistically possible, although it would be interesting. We are a reference center, performing the unofficial role of a national reference center and we have patients from all over the country who will never want or be able to come for a check-up. However, we also treat the complications related to the venous system. Complications of entry with a port or dialysis catheter are treated by cardiac surgeons (with variable success, as they can be lethal). For venous plastics and stenting, patients are referred to our facility with symptomatic obstructions caused by the implantation of an additional lead or catheter (dialysis, parenteral nutrition, but also a venous port).

Changes in the text: This is only the explanation to the Reviewer.

Comment 8: Is there any statistically significant relationship between the cumulative dwell lead time and the rate of venous obstruction?

Reply: There seems to be no relationship. Early occlusion is thrombosis that becomes fibrotic and results from endothelial injury during implantation. Late and very late occlusions are the result of, on the one hand, slowing down the blood flow and, on the other hand, moving the electrode in the venous system at the pace of the heart. The average age of the electrodes, and thus lead implant duration, in our material was: dwell time of the oldest lead per patient before TLE 103.40 months and cumulative dwell time of leads before TLE 15.63 years.

Changes in the text: It is only the explanation to the Reviewer.

Minor issues:

1. Title page, line 19: please specify number of figures and table.

Reply: Number of figures and tables was added to the title page

2. Methods section, line 99: delete “Mann Whitney U test” since it is not used for any analysis.

Reply: “Mann Whitney U test” was removed

3. Table 1, “Carlson’s index”, please correct with “Charlson comorbidity index”

Reply: It was corrected