Cardiovascular Pathology 24 (2015) 304–309

Contents lists available at ScienceDirect

Cardiovascular Pathology

Original Article

Method for sectioning and sampling hearts for histologic evaluation after delivery of biological agents by transendocardial injection

Deborah Vela [a,*], Amir Gahremanpour [b], L. Maximilian Buja [a,c]

[a] Cardiovascular Pathology Research Department, Texas Heart Institute at CHI St. Luke's Health–Baylor St. Luke's, Houston, TX, USA
[b] Stem Cell Center, Texas Heart Institute at CHI St. Luke's Health–Baylor St. Luke's, Houston, TX, USA
[c] The University of Texas Health Science Center at Houston, Houston, TX, USA

ARTICLE INFO

Article history:
Received 22 December 2014
Received in revised form 20 February 2015
Accepted 13 April 2015

Keywords:
Transendocardial injections
Electromechanical mapping
Pathology

ABSTRACT

The use of transendocardial (TE) injection as a validated method for delivering therapeutic agents to the diseased heart is increasing. Of the catheter systems currently available, TE injections guided by electromechanical mapping are attractive due to their minimal use of fluoroscopy and three-dimensional reconstruction capabilities that allow precise targeting of injections. We propose a method of cardiac sampling that takes advantage of the spatial accuracy of this system. Our preclinical experience with this methodology has yielded encouraging results, allowing a thorough examination of the injected areas through limited sampling.

1. Introduction

Over the past decade, the direct intramyocardial injection by catheter-based transendocardial (TE) access has been developed and implemented as a valid method for administering therapeutic agents to the diseased heart. This approach has been used primarily for the cardiac delivery of stem or progenitor cells, gene products, and growth factors. Moreover, the feasibility and safety of the technique has been validated in numerous preclinical studies [1–6] and in an increasing number of clinical studies [7].

TE injections can be performed under either fluoroscopic imaging or three-dimensional (3-D) electromechanical mapping (EMM) guidance. Left ventricular imaging under fluoroscopy provides a two-dimensional (2-D) image of a 3-D structure (the left ventricle) for the interventionalist. However, when navigating the TE injection catheter within the left ventricle under 2-D fluoroscopy images, localization and orientation of the catheter tip can be difficult, and precise targeting of specific areas inside the left ventricle can be unreliable. In contrast, EMM not only provides 3-D images for easier and more reliable catheter maneuvering but also permits discrimination between the underlying viable and nonviable myocardium in real time (see Section 2).

From a histological standpoint, the targeted nature of TE injections and the ability to plot them in a spatially accurate map provide a unique opportunity to locate and recover treated areas. This benefit, in turn, allows investigators to examine the interaction of the therapeutic agent with the surrounding host tissue. However, in large animal models, injection sites tend to be proportionally minuscule relative to the volume of heart tissue, and their location and recovery can be challenging. These small areas can be easily missed with the use of conventional or random sampling protocols and, thorough tissue sampling of the entire left ventricle, can be time consuming, labor intensive, and costly. In this article, we present our experience using a targeted method for localizing and recovering injection sites generated by TE injection. Given that our experience comprises sampling hearts in which treatments were administered exclusively by EMM-guided TE injections, we will first briefly describe the NOGA XP mapping system and the general characteristics of injection site histology.

2. NOGA navigation and mapping systems

NOGA technology was introduced in the mid 1990s as a method for 3-D nonfluoroscopic, electroanatomical mapping of the heart chambers [8–10]. To achieve this purpose, the NOGA system uses sensor-tipped navigation and mapping catheters to detect ultralow magnetic field sources. The current version of this system (NOGA XP Cardiac Navigation System, Biologics Delivery Systems, Diamond Bar, CA, USA) comprises three main components: a mapping catheter, a triangular location pad, and a companion workstation. With this system, investigators can acquire spatial, electrophysiological, and mechanical

Abbreviations: EMM, electromechanical mapping; LLS, local linear shortening; LVAD, left ventricular assist device; TE, transendocardial.

Conflicts of interest: None.

Funding: No outside sources provided any financial support for the conduct of the research and/or the preparation of the article, Method for sectioning and sampling hearts for histologic evaluation after delivery of biological agents by transendocardial injection.

* Corresponding author. Cardiovascular Pathology Research Department, Texas Heart Institute at CHI St. Luke's Health–Baylor St. Luke's, 6770 Bertner Avenue, MC 1-283, Houston, TX 77030, USA. Tel.: +1-832-355-9132; fax: +1-832-355-6812.
E-mail address: dvela@texasheart.org (D. Vela).

http://dx.doi.org/10.1016/j.carpath.2015.04.005
1054-8807/

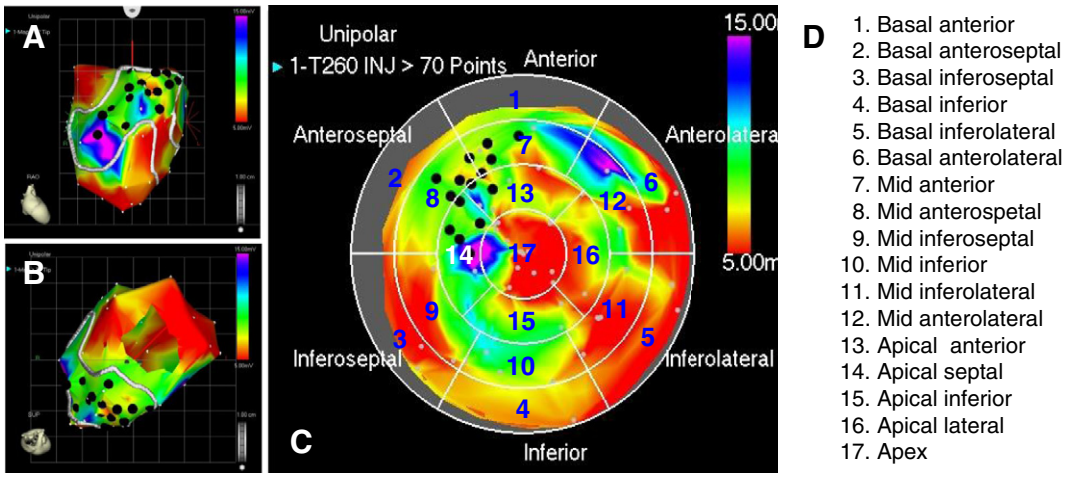

Fig. 1. 3-D and 2-D electromechanical ventricular maps and the 17-myocardial-segment scheme. 3-D left ventricular reconstruction maps from various views are used for navigation and injection in TE delivery. (A) and (B) show the 3-D unipolar maps in the right anterior oblique and superior views, respectively, of the left ventricle of a pig that received TE injections (*black dots*) in the mid apical anterior and anteroseptal walls. (C) The respective 2-D unipolar voltage map (bull's eye format) divided into a 17-segment scheme shows the injections clustered in only 4 of the segments. (D) Nomenclature for each of the 17 segments (15).

information from the endocardial surface of the left ventricle in real time. It is used predominantly in the left ventricle as a diagnostic and/or therapeutic tool [11].

The mapping catheter component (NogaStar mapping catheter, Biologics Delivery Systems) consists of a percutaneous 7-F catheter with a deflectable tip equipped with miniature magnetic sensors and standard electrodes for the detection of endomyocardial electrical signals. The triangular location pad is typically placed underneath the operating table and emits ultralow magnetic signals that are detected by the magnetic sensors on the mapping catheter to allow for the accurate location and orientation of the catheter tip [11]. The mapping catheter is typically introduced into the left ventricle retrograde through the aortic valve and is used to sample areas of the ventricular chamber progressively through the collection of a series of mapping points.

The information captured by the mapping catheter is transmitted to a companion workstation for processing and 3-D, color-coded reconstruction of the left ventricle [8,9]. The 3-D maps can also be converted into 2-D polar maps (bull's eye format) and divided into segments. The electrical activity is displayed as unipolar or bipolar voltage maps resulting from a surface electrocardiogram. The mechanical data is displayed as a local linear shortening (LLS) map that is based on the change in distance between two points from late diastole to maximum systole [10]. The injection component of the system usually consists of a modified mapping 8-F catheter equipped with a 27-G extendable needle for intramyocardial injection and a Luer fitting for connection to a conventional 1-ml syringe that is operated manually (MyoStar injection catheter, Biologics Delivery Systems) [10–12]. Needle extension can be calibrated from 1 to 10 mm (typically 4–5 mm) to achieve the desired depth of delivery of the injectate.

The utility of the NOGA system for evaluating regional viability of the myocardium has been examined in both preclinical [13–16] and clinical studies [17–19]. The ratios for endocardial voltage amplitude and LLS

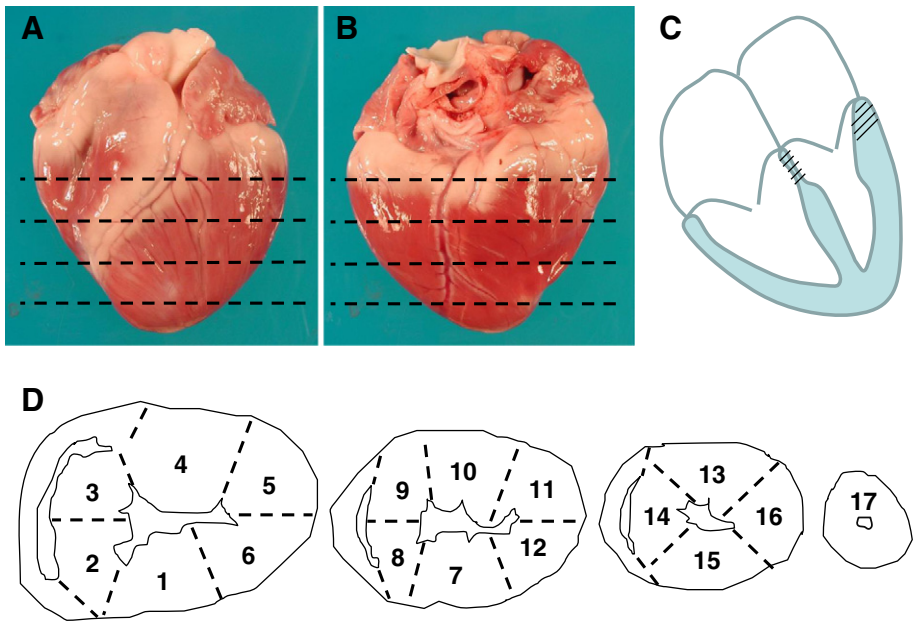

Fig. 2. Translation of the 17-segment polar plot into sectioning of the heart. (A and B) Anterior (A) and posterior (B) views of a pig heart. The dotted lines show 4 slices, parallel to the atrioventricular (AV) groove. (C) In the modification of the original 17-segment scheme used for tomographic imaging, the basal region is sampled only until reaching 1.5 cm below the AV groove. The portion at and immediately below the mitral valve is ignored (shaded area). (D) The resulting segments and their distribution within each heart slice.