# Studying cellular changes in heart attack scars associated with subsequent arrhythmias

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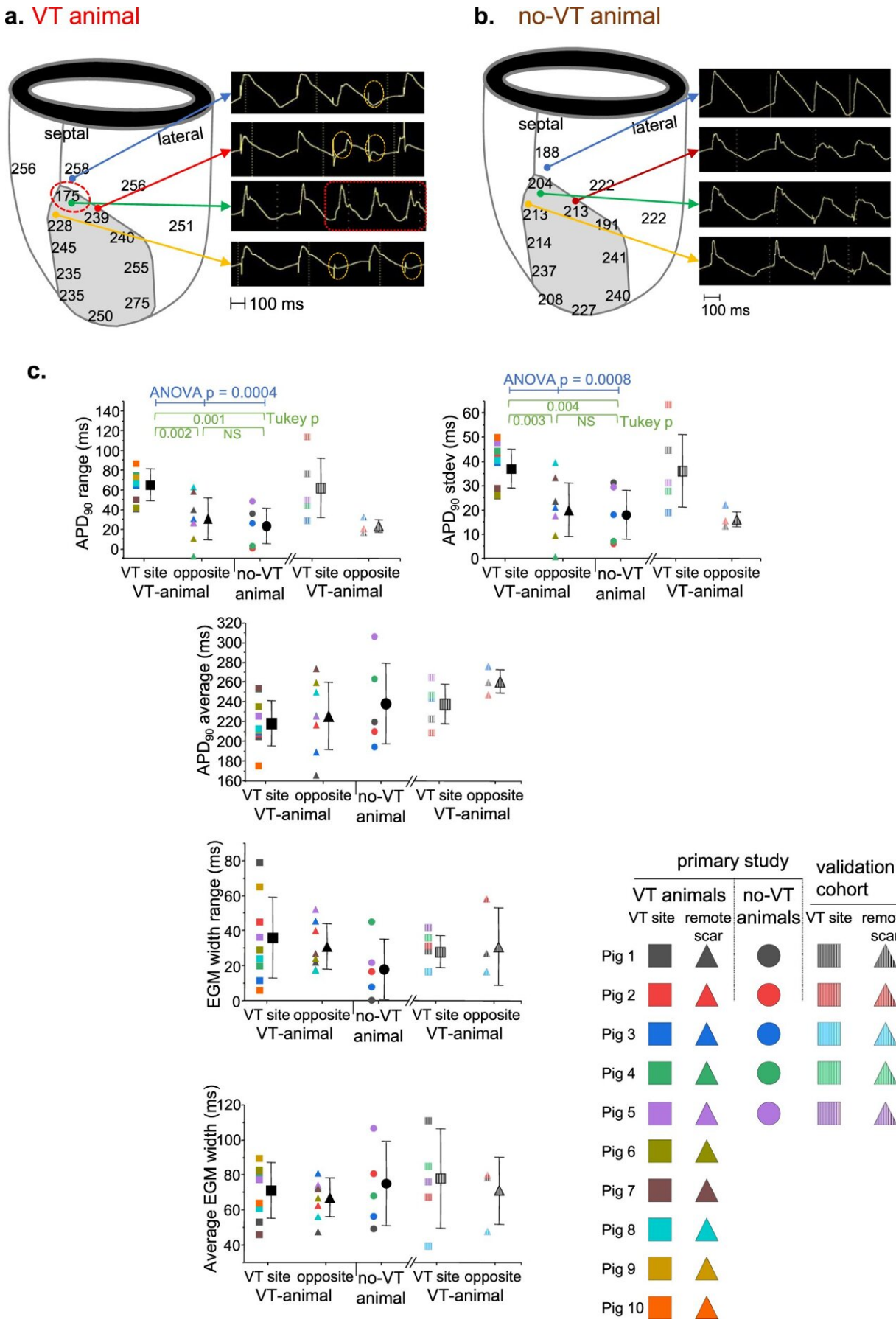
a. VT animal
septal
lateral
256
258
175
256
239
228
240
245
251
235
255
235
275
250
100 ms
b. no-VT animal
septal
lateral
188
204
222
213
213
191
222
214
241
237
208
227
240
100 ms
c.
ANOVA p = 0.0004
0.001
Tukey p
0.002
NS
APD90 range (ms)
VT site opposite VT-animal
no-VT animal
VT site opposite VT-animal
ANOVA p = 0.0008
0.004
0.003
NS
Tukey p
APD90 stdev (ms)
APD90 average (ms)
EGM width range (ms)
Average EGM width (ms)
primary study
VT animals
VT site
remote scar
no-VT animals
validation cohort
VT site
remote scar
Pig 1
Pig 2
Pig 3
Pig 4
Pig 5
Pig 6
Pig 7
Pig 8
Pig 9
Pig 10

Electrogram analysis from epicardial MAP and bipolar electrogram recordings during in vivo electrophysiology study. a APD90 at the indicated sites is shown in the left panel for a single VT animal. The gray region is the infarct scar. The red dashed circle is the location of the mapped VT circuit. The right panel shows MAP recordings illustrating the response to abrupt shortening of the pacing cycle length. Heterogeneity in response to the faster stimulus occurs with sites having conduction delay or block (orange circles) adjacent to a site with continued conduction (red box). b A similar map from a no-VT animal shows more homogeneous APDs and uniform conduction with abrupt pacing rate change. c Summary data comparing APD and bipolar electrogram width. The analysis from the VT animals included four adjacent electrograms each from the mapped VT site (square) and a site on the opposite side of the infarct scar from the VT site (triangle). In the no-VT animals (circle), we used four adjacent electrograms from a site anatomically matched to the VT site in the VT animals. n = 10 biologically independent animals in the VT group, five biologically independent animals in the no-VT group, and five biologically independent animals in the validation cohort. Data are reported as mean ± standard deviation. Data analysis included the Shapiro–Wilk test for normality followed by one-way ANOVA with the post-hoc Tukey test to assess differences. Source data are provided as a Source Data file. Credit: DOI: 10.1038/s41467-022-28418-1

UMass Chan researchers have published a study that brings new understanding to cellular changes in heart attack scars associated with subsequent arrhythmias, a leading cause of death. The paper, authored with scientists from Case Western Reserve University in Cleveland, Ohio, appears in the Feb. 11 issue of *Nature Communications*.

J. Kevin Donahue, MD, professor of medicine, director of electrophysiology research in the Division of Cardiovascular Medicine and a co-author of the paper, said the team found increases in two

proteins associated with changes in the heart's electrical function that explained the arrhythmias.

"With further development, these findings will help us identify people at risk for these abnormal heart rhythms and to fix this problem in people who have it," he said.

The research was conducted in pigs, whose hearts are almost identical to human hearts, Dr. Donahue said.

Heart muscle is damaged and becomes scarred following a heart attack. Investigators believed that there was something different about channels of heart muscle running through heart attack scars associated with arrhythmias, compared with scars with no arrhythmias.

"It was just the basic idea that we were going to start with a uniform playing field in which we're only comparing scar to scar, and inside of scar, and what we really want to know is what's special about the area where the arrhythmia comes from," said Donahue.

They identified two proteins, KCNE3 and KCNE4, that affected the electrical process of the heart's pumping. In scars with increased levels of these proteins, which supported ventricular arrhythmias, one side of a channel was resetting too slowly while the other side was too fast.

"And so, we realized that was the perfect setup for a particular type of arrhythmia, where it's a short circuit and it goes around and around through that loop," Donahue said.

"What we're doing next is we're looking at ways to use gene therapy to get rid of these two proteins," he said. "Also, we're looking for ways that we can develop a diagnostic test so that we can look at humans, see if they have a part of their heart attack scar that has this difference in the

resetting process, and then look to see if that's a way to identify people who are at risk."

**More information:** Kamilla Kelemen et al, Heterogeneous repolarization creates ventricular tachycardia circuits in healed myocardial infarction scar, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28418-1

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