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**Comparative effect of hypothermia and adrenaline
during cardiopulmonary resuscitation in rabbits**

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Running title: Intra-arrest hypothermia and cold saline infusion

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No conflict of interest

28 **Abstract (250 words)**

29 Introduction: Therapeutic hypothermia was shown to facilitate resumption of
30 spontaneous circulation (ROSC) when instituted during cardiac arrest. Here, we
31 investigated whether it directly improved the chance of successful resuscitation
32 independently of adrenaline administration in rabbits. We further evaluated the direct
33 effect of hypothermia on vascular function *in vitro*.

34 Methods: In a first set of experiments, four groups of anaesthetized rabbits were
35 submitted to 15 min of cardiac arrest and subsequent cardiopulmonary resuscitation
36 (CPR). The "Control" group underwent CPR with only cardiac massage and defibrillation
37 attempts. Two other groups received cold or normothermic saline infusion during CPR
38 (20 ml/kg of NaCl 0.9% at 4°C or 38°C, respectively). In a last group, the animals
39 received adrenaline (15 µg/kg i.v.) during CPR. In a second set of experiments, we
40 evaluated at 32 vs 38°C the vascular function of aortic rings withdrawn from healthy
41 rabbits or after cardiac arrest.

42 Results: In the first set of experiments, cardiac massage efficiency was improved by
43 adrenaline but neither by hypothermic nor normothermic saline administration. ROSC
44 was observed in 5/8 animals after adrenaline as compared to 0/8 in other groups.
45 Defibrillation rates were conversely similar among groups (7/8 or 8/8). In the second
46 set of experiments, *in vitro* hypothermia (32°C) was not able to prevent the dramatic
47 alteration of vascular function observed after cardiac arrest. It also not directly modified
48 vasocontractile nor vasodilating functions in healthy conditions.

49 Conclusion: In rabbits, hypothermia did not exert a direct hemodynamic or vascular
50 effect that might explain its beneficial effect during CPR.

51

52 **Key Words**

53 Cooling, Cardiac arrest, Ventricular fibrillation, Fluid, Cardiac massage, Animal Study.

54

55 **INTRODUCTION**

56 It is well admitted that therapeutic hypothermia (32°C-34°C) improves the prognosis
57 and the neurologic recovery of comatose survivors after cardiac arrest ¹⁻³. A maximal
58 neurological ⁴⁻⁷ and cardiovascular ⁸⁻¹⁰ protection is obtained when hypothermia is
59 started as soon as possible, e.g., using cold saline infusion during cardiopulmonary
60 resuscitation (CPR). The so-called “intra-arrest” hypothermia was shown to facilitate
61 resumption of spontaneous circulation (ROSC) in rodents and porcine models ^{6, 11}. Two
62 recent observational studies corroborate these results by the demonstration of a higher
63 frequency of ROSC in patients receiving hypothermia through cold saline infusion during
64 CPR as compared to standard care ^{12, 13}.

65 To our knowledge, the exact mechanism underlying the effect of therapeutic
66 hypothermia on ROSC remains still unknown but several hypotheses have been made. In
67 pigs, hypothermia was shown to improve the response to defibrillation attempts ^{6, 11} and
68 decrease the amount of adrenaline required to achieve ROSC ⁶. Hypothermia was also
69 reported to improve systemic hemodynamics by increasing arterial resistances ¹⁴. In
70 animal models, the influence of hypothermia on vessel function and hemodynamics was
71 however investigated when combined to adrenaline, which could alter the exact role
72 played by therapeutic hypothermia ^{6, 15-17}. The aim of the present study was to
73 investigate the intrinsic vascular effect of hypothermia during CPR. Accordingly, we
74 investigated the effect of therapeutic hypothermia induced by cold saline infusion on
75 cardiac massage efficiency in rabbits without adrenaline administration. In order to
76 determine the real effect of hypothermia versus that of fluid loading, we compared cold
77 saline to warm saline infusion. We finally included a group with adrenaline
78 administration alone, as a positive control of efficient CPR. Our end-points were cardiac
79 massage efficiency assessed by hemodynamic parameters, rate of defibrillation success

80 and ROSC occurrence. In addition, we also examined the direct effect of hypothermia
81 (32°C vs 38°C) on the vascular response of isolated vessels after cardiac arrest in
82 rabbits.

83

84 MATERIALS AND METHODS

85 The animal instrumentation and the ensuing experiments were conducted in
86 accordance with French official regulations, after approval by the local ethical
87 committee (ComEth AnSES/ENVA/UPEC n°16).

88 Animal preparation and cardiac arrest procedure

89 Male New Zealand rabbits (2.5-3.0 kg) were anaesthetized using zolazepam,
90 tiletamine and pentobarbital (all 20-30 mg/kg i.v.). After intubation and initiation of
91 mechanical ventilation ($FiO_2 = 30\%$), two central catheters were inserted in the carotid
92 artery and jugular vein for measurements of central arterial and venous pressures,
93 respectively. Two electrodes were implanted upon the chest and inserted into the
94 oesophagus. After a period of stabilization, ventricular fibrillation was induced by an
95 alternative current (10 V, 4 mA) between the two electrodes. Mechanical ventilation was
96 stopped throughout the cardiac arrest period. After 15 min of untreated cardiac arrest,
97 CPR was initiated using cardiac massage (~200 beats/min) and restoration of a
98 continuous oxygen flow ($FiO_2=100\%$). Electric attempts of defibrillations (10 J/kg) were
99 started at the 3rd min of CPR and repeated every 2 min until ROSC, which was considered
100 as an organized cardiac rhythm with a systolic arterial pressure above 40 mmHg during
101 at least 1 min.

102 Experimental protocol

103 In addition to basic life support and electric attempts of defibrillation, rabbits were
104 randomly assigned to one experimental group (Figure 1A). The Control group did not
105 receive any additional procedure. In the “Saline 4°C” and “Saline 38°C” groups, the
106 animals received 20 ml/kg of NaCl (0.9% at 4°C or 38°C, respectively) from the 1st to the
107 3rd min of CPR. The last group received bolus administrations of adrenaline (15 µg/kg
108 i.v.) every 2 min until occurrence of ROSC. In the Control group, as well as in “Saline 4°C”

109 and “Saline 38°C” groups, no any vasopressor drug was used. Resuscitation efforts were
110 stopped after 10 min of unsuccessful CPR or in case of haemoptysis.

111 Throughout the protocol, rectal, oesophageal and tympanic temperatures were
112 monitored using thermal probes (Harvard Apparatus, Paris, France). Hemodynamic
113 parameters were also continuously recorded using external electrocardiogram, arterial
114 and venous blood pressures in the right carotid and jugular vein, respectively. The
115 difference between arterial and venous pressures was calculated with the data
116 acquisition software HEM version 3.5 (Notocord, Croissy-sur-Seine, France). End-tidal
117 CO₂ concentration in the expired air (EtCO₂) and blood oxygen saturation (SpO₂) were
118 continuously assessed. The primary end-point of the study was the percentage of
119 animals achieving ROSC in each group. Defibrillation success and hemodynamic
120 parameters were secondary end-points.

121 *In vitro analysis of vascular function*

122 Additional rabbits were anaesthetized and intubated as described above. They were
123 randomly submitted to a “Sham” procedure without any cardiac arrest or to 15 min of
124 untreated ventricular fibrillation as previously described. In the latter case, animals
125 were resuscitated using cardiac massage, electric attempts of defibrillation and
126 adrenaline administration. After ROSC, the animals were monitored during 6 hours with
127 constant adrenaline infusion in order to avoid hypotension if necessary. If necessary,
128 anesthesia was maintained using pentobarbital administration. Animals were then
129 euthanized and the descending thoracic aorta was removed and cleaned of connective
130 tissues. Aorta rings were mounted in isolated vessels chambers, as previously
131 described¹⁸. After 120 min of equilibrium under resting tension of 2 g, the chamber
132 temperature was randomly adjusted at either 32°C or 38°C. Thirty minutes later, the
133 response to increasing concentrations of noradrenaline was evaluated (0.3, 1 and

134 3 $\mu\text{mol/L}$). The endothelial-dependent and independent relaxation was then assessed
135 using acetylcholine (0.1 mmol/L) and sodium nitroprusside (0.1 mmol/L), respectively.
136 The experiments were repeated at two levels of temperature (32 or 38°C).

137 *Statistical analysis*

138 Data were expressed as mean \pm SEM. Temperatures, hemodynamic and *in vitro*
139 parameters were compared between the different groups using a two-way ANOVA for
140 repeated measures followed by a Fisher LSD post-hoc analysis. The time to achieve
141 successful defibrillation were compared between groups using a log-rank test. A similar
142 analysis was used for the time to ROSC. The rate of successful defibrillation and ROSC
143 were compared using a Chi-square test. The corresponding Kaplan-Meier curves were
144 drawn. Significant differences were determined at $p\leq 0.05$.

145

146 **RESULTS**147 *In vivo investigations*

148 Thirty-two rabbits were randomly included in the different groups (n=8 in each
149 group). As illustrated in Figure 1B, the esophageal, tympanic and rectal temperatures
150 were not significantly different among groups at baseline. During CPR, a significant and
151 expected decrease was observed for oesophageal and tympanic temperatures in the
152 “Saline 4°C” group as compared to all other groups. The rectal temperature was still not
153 significantly different among the 4 groups.

154 As shown in Table 1, hemodynamic parameters, SpO₂ and EtCO₂ were not different
155 among groups at baseline. After the onset of CPR, cardiac massage efficiency was greater
156 in the “Adrenaline” group as compared to the 3 other groups as evidenced by a
157 significant increase in arterial blood pressure and in the maximal difference between
158 arterial and venous pressures. These parameters were conversely not significantly
159 modified in the two “Saline” groups as compared to the “Control” group.

160 As illustrated in Figure 2, electric attempts of defibrillation led to a high and similar
161 rate of successful defibrillation in all groups (7/8 animals in the “Control”, “Saline 4°C”
162 and “Adrenaline” groups; 6/8 in the “Saline 38°C” groups, respectively). However, no
163 animal elicited successful ROSC in the “Control”, “Saline 4°C” and “Saline 38°C” whereas
164 5/8 rabbits achieved ROSC in the “Adrenaline” group. In the “Saline 38°C” group,
165 resuscitation efforts were interrupted in 3 rabbits after occurrence of haemoptysis.

166 *In vitro investigations*

167 Experiments were conducted in 15 and 14 aorta rings sampled from 3 rabbits under
168 sham condition and 4 others after cardiac arrest, respectively. In the rabbits submitted
169 to cardiac arrest, the total dose of adrenaline administered *in vivo* before euthanasia was
170 990±179 µg/kg. As illustrated in Figure 3A, the noradrenaline administration induced a

171 concentration-dependent contraction *in vitro* in all groups. This effect was however
172 significantly attenuated after cardiac arrest as compared to sham condition but this was
173 not modified by temperature (32 vs 38°C). The endothelium-dependent relaxation in
174 response to acetylcholine was also significantly altered after cardiac arrest but remained
175 unchanged regardless the chamber temperature (figure 3B). Endothelium-independent
176 relaxation after sodium nitroprusside administration was maximal and identical in all
177 conditions.

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181 **DISCUSSION**

182 The present study demonstrates that hypothermia induced by cold saline infusion
183 neither affected defibrillation success, ROSC frequency nor cardiac massage efficiency in
184 rabbits. Pure fluid loading through warm saline infusion was also inefficient whereas
185 adrenaline administration improved cardiac massage efficiency and rate of ROSC. To our
186 knowledge, this is the first study to specifically address the effect of cold or warm fluid
187 loading with no concomitant administration of adrenaline during CPR in animals.
188 Previous studies rather investigated the role of hypothermia “on top of” adrenaline
189 administration ^{6, 8, 11, 15, 19-22}. In our experimental conditions, mild hypothermia did also
190 not affect vessel reactivity in isolated aorta after cardiac arrest.

191 The most important finding of this study is the lack of effect of hypothermia on ROSC
192 occurrence when applied alone, *i.e.*, without adrenaline administration. In a recent
193 review, Scolletta et al. showed that hypothermia conversely facilitates ROSC in pigs and
194 rodents when it was combined to adrenaline administration ¹⁹. The rate of ROSC was for
195 example improved with cold blanket cutaneous application ¹¹, cold saline infusion ⁶,
196 hypothermic liquid ventilation ^{15, 20}, trans-nasal evaporation cooling ^{21, 22} or
197 endovascular cooling ⁸ in pigs. Interestingly, this was often attributed to defibrillation
198 facilitation during hypothermia ^{6, 11}. As example, Boddicker *et al.* demonstrated that
199 hypothermia dramatically improved the chance of defibrillation in a swine model of
200 refractory ventricular fibrillation ¹¹. Menegazzi *et al.* also demonstrated that
201 hypothermic CPR reduced the decay of ECG waveforms and subsequently improved the
202 rate of successful defibrillation ⁶. In our study, it was not possible to show a similar
203 benefit since the rate of successful defibrillation was virtually maximal in Control
204 conditions.

205 Another apparent discrepancy is the lack of effect of hypothermia on cardiac
206 massage efficiency, as observed in a previous pig study ¹⁵. Indeed, neither cold saline
207 infusion nor normothermic fluid loading were able to affect hemodynamic parameters
208 during CPR. This could be in part related to the proper effect of fluid loading which could
209 compromise the direct effect of cardiac hypothermia. Indeed, Riter et al. showed that a
210 load-independent cooling strategy (hypothermic liquid ventilation) could improve
211 coronary perfusion pressure during CPR as compared to cold saline infusion. In our
212 study, the appearance of several cases of haemoptysis also suggests a poor tolerance of
213 fluid loading after warm saline infusion. It was not possible to directly assess coronary
214 perfusion pressure in the present study since this is technically challenging in the rabbit
215 model ^{15, 23, 24}. The difference between arterial and venous central pressures could
216 however be considered as an indirect evaluation. In accordance with the previous
217 findings of Riter et al. ¹⁵ in pigs, it was not modified by hypothermic fluid loading, this is
218 actually in accordance.

219 In the present study, we did not investigate the combined effect of hypothermia and
220 adrenaline *in vivo* as the latter was too efficient by itself. Any improvement in the rate of
221 ROSC would therefore be hard to evidence in such experimental conditions. We
222 proposed to address this issue *in vitro* through the determination of the temperature
223 effect on the vascular response to adrenergic stimulation. These experiments clearly
224 showed a lack of effect of temperature (32 vs 38°C) on the vascular response to
225 noradrenaline, while cardiac arrest dramatically altered vascular function. The latter
226 result could be either attributed to tachyphylaxis and desensitization after adrenaline
227 administration or to an actual vascular dysfunction, as described regarding
228 microcirculation in patients after cardiac arrest ²⁵. With lower temperatures, Mustafa
229 and Thulesius interestingly showed that profound hypothermia (27°C and 10°C) altered

230 the response to noradrenaline of isolated carotids arteries ¹⁶. The cutaneous application
231 of low temperatures (e.g., ice packs) is also well known to induce superficial
232 vasoconstriction ^{14, 26}.

233 In conclusion, cold saline infusion in the absence of adrenaline administration did
234 not improve ROSC occurrence in rabbits. One could speculate that fluid loading hidden
235 the beneficial effect of temperature reduction in this model.

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331 **Table 1:** Hemodynamic parameters

332

	Baseline				Cardiopulmonary resuscitation (t=3 min)			
	Control	Saline 4°C	Saline 38°C	Adrenaline	Control	Saline 4°C	Saline 38°C	Adrenaline
<u>Heart rate (beats/min)</u>								
	256±7	260±9	254±8	260±8	244±7	242±8	245±11	251±7
<u>Arterial pressure (mmHg)</u>								
Max	103±7	104±4	102±3	107±4	62±2	57±4	51±3	92±11 *
Mean	83±10	84±7	89±4	90±5	26±2	30±7	25±1	51±6 *
Min	72±10	70±4	78±4	79±5	2±2	6±2	6±1	19±9 *
<u>Venous pressure (mmHg)</u>								
Max	6±1	6±1	4±1	5±1	57±10	38±9	54±13	60±11
Mean	4±1	5±1	3±1	3±1	22±3	18±4	17±4	16±4
Min	2±1	3±1	1±1	1±1	-1±1	2±2	-4±3	-3±2
<u>Maximal difference between arterial and venous pressure (mmHg)</u>								
	101±6	98±4	99±3	106±4	36±4	28±8	33±5	69±11 *
<u>End-tidal CO₂ concentration in the expired air (mmHg)</u>								
	43±7	38±2	40±2	35±5	21±7	19±3	18±2	19±2
<u>Blood oxygen saturation (%)</u>								
	100	99±1	100	99±1	76±9	71±5	79±4	78±6

333

334 *, p<0.05 vs all other groups

335

336 **LEGEND OF FIGURES**

337

338 **Figure 1:** Experimental protocol and body temperatures.339 *Panel A: Schematic representation of the experimental protocol. Animals were randomly*340 *assigned to the following groups: "Control", "Saline 4°C" (20 ml/kg of cold NaCl 0.9% i.v.),*341 *"Saline 38°C" (20 ml/kg of warm NaCl 0.9% i.v.), or "Adrenaline" (boluses of 15 µg/kg i.v.).*342 *Panel B: Body temperatures throughout protocol in the different groups.*343 *CPR, cardiopulmonary resuscitation; Temp., temperature; VF, ventricular fibrillation; *,*344 *p<0.05 between "Saline 4°C" and all other groups.*

345

346 **Figure 2:** Rate and frequency of successful defibrillation and resumption of spontaneous347 *circulation (ROSC).*348 *Panel A: Overall frequency of successful defibrillation, ROSC and haemoptysis appearance*349 *during cardiopulmonary resuscitation efforts.*350 *Panel B: Rate and frequency of successful defibrillation during cardiopulmonary*351 *resuscitation efforts.*352 *Panel C: Rate and frequency of ROSC during cardiopulmonary resuscitation efforts.*353 **, p<0.05 vs all other groups.*

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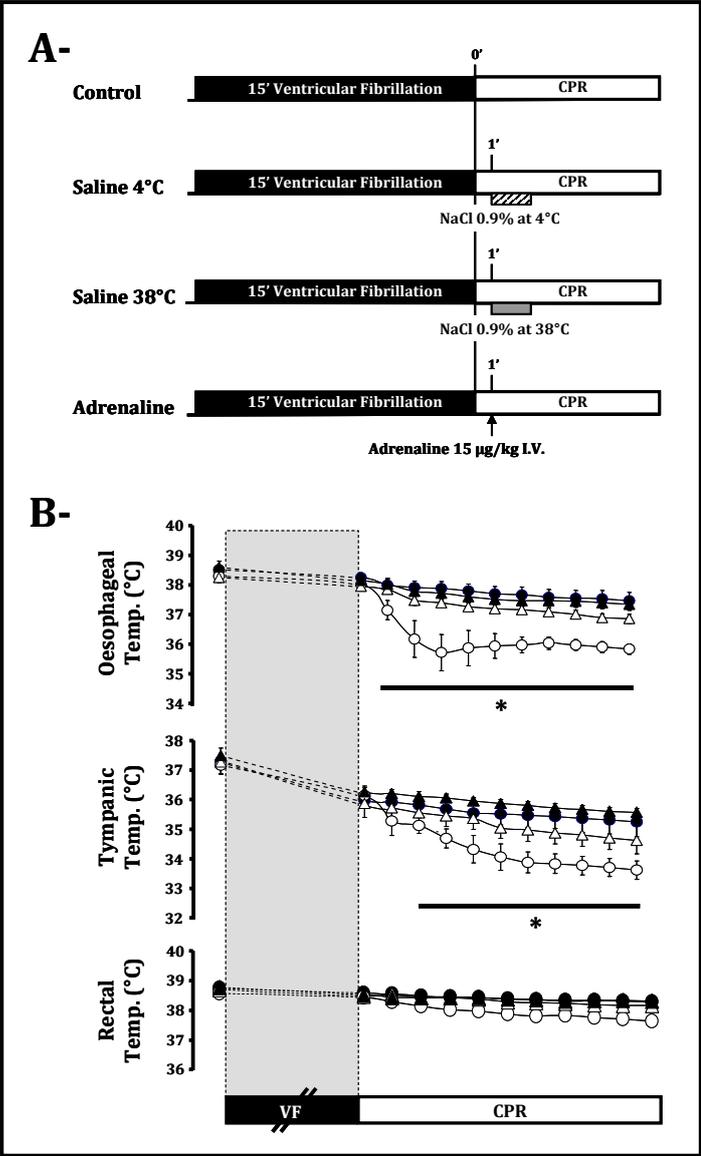
355 **Figure 3:** In vitro investigations at two different temperatures (32 vs 38°C) of the356 *vascular function of aorta rings sampled from healthy rabbits (Sham groups) or after*357 *cardiac arrest*358 *Panel A: Contraction of the aorta rings in response to increasing concentrations of*359 *noradrenaline (tension expressed in g).*

360 *Panel B: Vasodilating response to acetylcholine and sodium nitroprusside (expressed*
361 *in % of the maximal contraction induced by noradrenaline).*

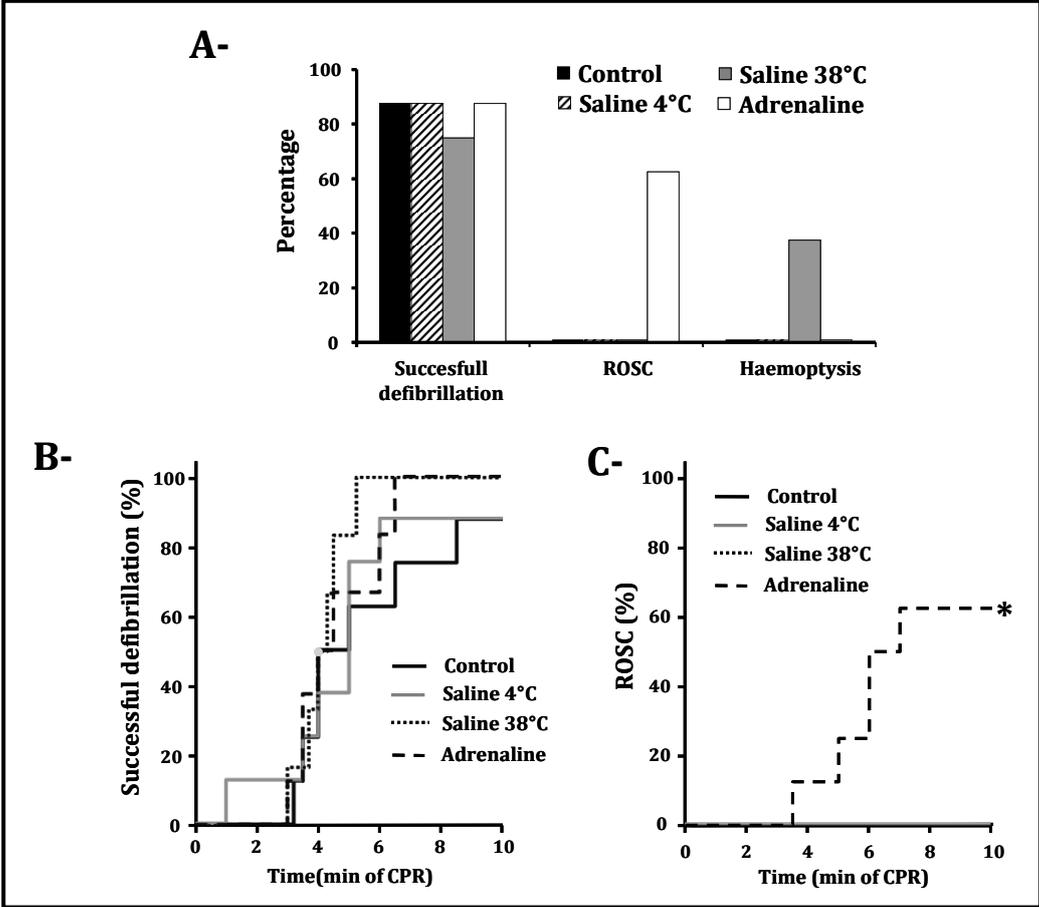
362 **, $p < 0.05$ vs Sham at the same temperature.*

363

364 Figure 1
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366 Figure 2
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368 **Figure 3**
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 370

