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Increased Sensitivity to Thermal Pain and Reduced Subcutaneous Lidocaine Efficacy in Redheads

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Abstract

Background: Anesthetic requirement in redheads is exaggerated, suggesting that redheads may be especially sensitive to pain. We therefore tested the hypotheses that women with natural red hair are more sensitive to pain, and that redheads are resistant to topical and subcutaneous lidocaine.

Methods: We evaluated pain sensitivity in red-haired (n=30) or dark-haired (n=30) women by determining the electrical current perception threshold, pain perception, and maximum pain tolerance with a *Neurometer CPT/C* (Neurotron, Inc., Baltimore, MD). We evaluated the analogous warm and cold temperature thresholds with the *TSA-II Neurosensory Analyzer* (Medoc Ltd., Minneapolis, MN). Volunteers were tested with both devices at baseline and with the *Neurometer* after 1-hour exposure to 4% liposomal lidocaine and after subcutaneous injection of 1% lidocaine. Data are presented as medians [interquartile ranges].

Results: Current perception, pain perception, and pain tolerance thresholds were similar in the red-haired and dark-haired women at 2000, 250, and 5 Hz. In contrast, redheads were more sensitive to cold pain perception (22.6°C [15.1, 26.1] vs. 12.6°C [0, 20], $P=0.004$), cold pain tolerance (6.0°C [0, 9.7] vs. 0.0°C [0.0, 2.0], $P=0.001$), and heat pain (46.3°C [45.7, 47.5] vs. 47.7°C [46.6, 48.7], $P=0.009$). Subcutaneous, lidocaine was significantly less effective in redheads, e.g., pain tolerance threshold at 2000 Hz stimulation in redheads was 11.0 mA [8.5, 16.5] vs. >20.0 mA [14.5, >20] in others, $P=0.005$).

Conclusion: Red hair is the phenotype for mutations of the melanocortin 1 receptor. Our results indicate that redheads are more sensitive to thermal pain and are resistant to the analgesic effects of

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Summary Statement: Redheaded women are more sensitive to thermal pain than women with dark hair and are resistant to the analgesic effects of subcutaneous lidocaine. These findings extend the previous observation that redheads are resistant to volatile anesthetics. Mutations of the melanocortin 1 receptor, or as a consequence thereof, therefore seem to modulate pain sensitivity.

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Introduction

Red hair nearly always results from mutations of melanocortin-1 receptor gene (*MC1R*).¹⁻³ The human melanocortin-1 receptor (MC1R) is expressed on the surface of melanocytes and is a key regulator of intracellular signaling to the melanin biosynthetic pathway governing pigment formation. In general, the balance of pheomelanin (yellow-red) and eumelanin (dark brown) pigments determines hair and skin color in the Caucasian population.⁴ The red hair phenotype results from excess pheomelanin production due to dysfunctional MC1Rs.^{5,6} In contrast, when a normal (consensus) MC1R is expressed, the predominant pigment produced by melanocytes is eumelanin resulting in a high eumelanin to pheomelanin ratio.

In a previous study, we found that women with red hair required 19% more desflurane to suppress movement in response to noxious electrical stimulation than women with dark hair, making red hair a distinct phenotype associated with anesthetic requirement in humans.⁷ The effects of human MC1R dysfunction on anesthetic requirement were further supported by the finding that anesthetic requirement is slightly, but significantly, increased in melanocortin-1 receptor knockout mice.⁸ And finally, the recent work of Mogil *et al.* also suggests involvement of MC1R in pain modulation.⁹

MC1R expression has been identified in human pituitary tissue, glial cells, and in cells of the human periaqueductal gray matter.^{10,11} However, the central nervous system is not a major site of *MC1R* expression.⁶ It thus remains unclear why *MC1R* mutation should alter anesthetic requirement. Because anesthetic requirement in previous studies was measured in the context of a response to a noxious stimulus, these results suggest that MC1R dysfunction could possibly modulate a response to any stimulus that might be perceived as painful. A possible explanation is that *MC1R* mutation upregulates production of the receptor's primary ligands, melanocortins including α -MSH, which also stimulates other melanocortin receptors — including the melanocortin 4 receptor that modulates cold and mechanical allodynia in a rat neuropathic pain model.¹²

To the extent that this theory is correct, one might expect baseline pain sensitivity to be exaggerated in redheads. Anecdotal reports support this theory: after reports of our previous study⁷ appeared in the lay press, we received more than a hundred communications from redheads who claimed that anesthesia often failed or that unusually large doses of local anesthetics were required to achieve adequate analgesia. We therefore tested the hypotheses that natural redheads are more sensitive to pain than women with dark hair and that redheads are resistant to topical and subcutaneous lidocaine.

Materials and Methods

With institutional approval and informed written consent, we studied healthy (ASA I) female Caucasian volunteers aged 18 to 40 years who had either natural bright red, black, or dark brown hair. We considered volunteers to be Caucasian if they reported being primarily of northern European descent. Volunteers were monetarily reimbursed for their time.

Other studies indicate that women report different pain experiences and more negative responses to pain than men,^{13,16} as well different responses to analgesics.¹⁷ We thus restricted our study population to women. A higher sensitivity to pain stimuli has been observed during the luteal phase of the menstrual cycle.^{18,19} We therefore also restricted studies to the first ten days of the participants' menstrual cycles unless they were using hormonal contraceptives.

Exclusion criteria included chemical hair treatment, any history of medical or psychiatric problems, history of current or past chronic pain conditions, skin abrasions or lesions on testing sites, pregnancy, body mass index $>30 \text{ kg/m}^2$, recreational drug use, or use of medications other than oral contraceptives. Based on the means and standard deviations obtained from preliminary test results on the *Neurometer CPT/C* device (Neurotron, Inc., Baltimore, MD),²⁰ an a priori sample-size estimate suggested that eighteen subjects in each group would provide a 90% power for detecting a 40% reduction in pain tolerance thresholds at a two-tailed, unpaired alpha level of 0.05. We thus enrolled 30 volunteers with red hair and 30 with dark hair.

All studies were started at 8:00 am. Volunteers fasted and refrained from smoking for at least eight hours before the start of the protocol. Studies were conducted in a quiet room that was maintained at a comfortable ambient temperature. Each volunteer's height, weight, and age were recorded. Sensory and pain thresholds for each volunteer were tested with two devices: the *Neurometer CPT/C* (Neurotron, Inc., Baltimore, MD) and the *TSA-II Neurosensory Analyzer* (Medoc Ltd., Minneapolis, MN).

The *Neurometer CPT/C* produces a biphasic sinusoid alternating current (AC) waveform stimulus at frequencies of 2000, 250, and 5 Hz.^{20,21} Sinewaves at 2000, 250, and 5 Hz correspond to depolarization periods of 0.25 msec, 2 msec, and 100 msec, respectively. The large diameter fibers can respond to the rapid 2000 Hz stimulus while the small unmyelinated fibers require several milliseconds of a continuous depolarization period to respond. However, large fibers repolarize faster than the slow increase of the 5-Hz stimulus can depolarize them and therefore do not achieve threshold potential with that stimulation. Together, these factors result in the 2000, 250 and 5 Hz sinewave depolarizations selectively evoking responses from the large myelinated A-beta, the small myelinated A-delta, and the small unmyelinated C fibers, respectively.^{22,23} The *Neurometer* automatically compensates for alterations in skin resistance by adjusting the voltage to maintain a constant current.²¹ Our *Neurometer* was modified to deliver currents from zero to a maximum of 20 mA (milliampere).

For determination of the baseline sensory, pain perception, and pain tolerance thresholds, pairs of gold electrodes were positioned on glabrous skin of both the right and left ring fingers. For each specific threshold measurement, both sides (dominant and non-dominant hand) were tested sequentially, with the order determined by random assignment. The skin was prepared for testing with a gentle abrasive cleaning preparation. A pair of gold electrodes (1 cm diameter) separated by a 1.7 cm Mylar spreader was coated with a thin layer of chloride-free electroconductive gel and taped to the finger. Volunteers were instructed as to how to respond to each stimulus according to a standardized script and were blinded at all times to the threshold measurement results displayed on the *Neurometer* device.

The baseline current perception (sensory) thresholds were tested first at 2000, 250 and 5 Hz. The operator slowly increased the stimulus until the volunteer consistently reported detecting the stimulus at 0.02 mA value and not detecting the stimulus 0.2 mA units below this value. The manual intensity alignment was followed by auto test cycles controlled by the device. Auto test cycles with true or false testing confirmed that the volunteer responses were within ± 0.04 mA. After repeated and consistent crossovers occurred, the device determined the exact mA current value.

After completing the baseline current perception threshold measurements on both hands, baseline pain perception thresholds and then pain tolerance thresholds were measured on both hands. For pain perception and pain tolerance threshold measurements, the volunteer initiated the stimulation by pushing a button on the device. As long as the volunteer depressed the button, the amount of stimulation slowly increased automatically. We asked volunteers to release the

button when they perceived the stimulus as painful (for pain perception thresholds) or it became intolerable (for pain tolerance thresholds). We allowed at least two minutes, or until sensation in the finger had returned to baseline, between successive stimuli. In summary, three different frequencies of stimulation (2000 Hz, 250 Hz, and 5 Hz) were used in order to obtain three different threshold measurements (current perception, pain perception, and maximum pain tolerance). These baseline sensory and pain thresholds in response to electrical stimulation were normally distributed.

In order to determine baseline thermal sensory, pain perception, and pain tolerance thresholds, contact heat stimuli were delivered using a computer-controlled thermal sensory analyzer (*TSA-II Neurosensory Analyzer*). This device has been used extensively for quantitative assessment of thermal sensory and pain thresholds.^{18,24} The maximum delivered temperature was 50°C, and the minimum temperature was 0°C.

For temperature threshold testing, a 3 x 3 cm square thermode was positioned on the volar area of the volunteer's forearm. Both the dominant and non-dominant arms were tested sequentially, with the order determined randomly. From a baseline of 32°C, probe temperature was increased or decreased at a rate of 0.5°C/second until the volunteer responded. The slow rise presumably evokes mainly stimulation of C-nociceptive afferents.²⁵ Volunteers were instructed as to how to respond to each stimulus according to a standardized script and were always blinded to results. Four trials of warm and cold sensory thresholds were given to each volunteer, followed by four trials of heat pain and cold pain (perception) thresholds and then four trials of heat pain and cold pain tolerance thresholds. Volunteers were instructed to press a button to interrupt the stimulus whenever they felt that the appropriate threshold had been reached. The four trials were averaged to determine the thresholds. A few volunteers reported mild tenderness at the testing site after maximum intensity stimulation; in these volunteers, the position of the thermode was altered slightly between trials in order to avoid either sensitization or habituation of cutaneous receptors. In addition, we allowed at least 60 seconds between successive stimuli. Subjects were blinded at all times to the temperature threshold values obtained with the *TSA-II Neurosensory Analyzer*.

In addition to the baseline current and thermal threshold measurements, we also investigated how the pain tolerance thresholds were affected by local anesthetic. The methodology to evaluate the sensitivity to different local anesthetics using the *Neurometer* has been described in previous studies.^{17,26} Briefly, the volar surface of the non-dominant forearm of the volunteer was divided into three areas, each measuring approximately 2 x 4 cm. One area functioned as control; the second area was covered with a 6-mm-thick layer of 4% liposomal lidocaine (ELA-Max, Ferndale laboratories, Ferndale, MI), which was wiped clean after 60 minutes. In a previous study, the average onset time for this formulation of lidocaine was 7 minutes,²⁶ the application time of 60 minutes in this study should therefore be sufficient to provide cutaneous anesthesia. In the third area, we injected 2 mL of 1.0% lidocaine subcutaneously and allowed an onset time of at least 5 minutes.

Pain tolerance threshold values were determined at frequencies of 2000 Hz, 250 Hz, and 5 Hz as described above for all three areas. Subjects were blinded to the pain tolerance threshold values generated for each area. Pain tolerance thresholds of areas tested for local anesthetic sensitivity were found to have a censored outcome, i.e. many volunteers reached maximum pain tolerance thresholds and could go no higher.

Data Analysis

We compared the demographics and other volunteer characteristics with unpaired, two-sided, t-tests for continuous variables and chi-square or Fisher's exact test for categorical variables. The analysis of perception and threshold outcomes and all continuous outcomes depended on

the distribution of the data and whether any of the values were censored. Values were considered censored when the maximum possible pain threshold values were not reached, i.e., the maximum possible pain threshold values in these volunteers were a function of the limits of the Neurometer device (max. output is 20 mAmps) and not a physical limitation. In other words, the actual pain threshold values were not known because the values were truncated or “right censored” at 20 mAmps. Outcomes that were normally distributed were compared with unpaired, two-sided, t-tests. If the values were skewed, the Mann-Whitney rank-sum test was used for comparing the groups. If some of the data were censored, then we used Kaplan-Meier survival curves and log-rank tests. $P < 0.05$ was considered statistically significant.

Results

Demographic and morphometric characteristics of the redheaded and dark-haired volunteers were similar (Table 1). Baseline thresholds for the dominant and non-dominant arms were also similar; values from each arm were thus averaged. None of the baseline responses to electrical stimulation (*Neurometer*; current perception, pain perception, or pain tolerance thresholds) differed significantly between the two groups (Table 1).

In contrast, baseline threshold responses to thermal stimuli were different between the groups: redheads were more sensitive to cold pain, both in terms of cold pain perception and cold pain tolerance (Table 2)). Although the difference in heat pain perception between the two groups did not reach statistical significance, redheads had a lower threshold for heat pain tolerance (Table 2).

Liposomal lidocaine was slightly, but not significantly, less effective in redheads (Table 3). In contrast, subcutaneous lidocaine was significantly less effective in redheads than in subjects with dark hair: Median survival thresholds for pain tolerance (Table 3) were lower in red-haired than in dark-haired volunteers (Fig. 1).

Discussion

The range of the baseline current perception, pain perception and pain tolerance thresholds in this study was consistent with those reported in earlier studies using test sites on the fingers²⁷ or the volar surface of the forearm.²⁶ Although we measured considerably lower pain tolerance thresholds on the forearm test sites compared to the finger test sites, this difference is consistent with the difference observed in other studies when different test sites were used.^{26,27} This merely seems to indicate that the absolute range of the threshold measurements will depend on the location of a particular test site. The highest values for each threshold were obtained with electrical stimulation at 2000 Hz and the lowest values with a 5-Hz stimulation, consistent with previous observations.²⁶ Nonetheless, we were unable to detect any differences in baseline sensory, pain perception, or pain tolerance thresholds in response to electrical stimuli between women with red or dark hair.

Baseline heat pain perception and heat pain tolerance threshold values in this study corresponded well to those reported in previous studies.^{16,18,24} We found that redheads were significantly more sensitive to cold pain perception, cold pain tolerance, and heat pain tolerance. Heat pain perception threshold was also lower, but not significantly so, in redheads. In contrast to the pain tolerance thresholds, the heat sensory perception threshold was actually higher in redheads.

Interestingly, our baseline responses to thermal stimuli contrast with those reported by Mogil *et al.*,⁹ in which no group differences were reported in ischemic pain perception thresholds, ischemic pain tolerance thresholds, or thermal pain intensity ratings as a function of hair color.⁹ Methodological differences are a possible explanation: in Mogil's study, a series of

suprathreshold thermal stimuli consisting of ten heat pulses at 52°C were applied and the subjects rated the intensity of each pulse on a scale of 0-100. The ratings were then combined to obtain a score for thermal pain intensity. Despite the fact that such scales have fixed endpoints, a limitation in the use of this and other such scales is the fact that these endpoints are entirely based upon a subject's previous subjective experiences. The use of rating scales possibly leads to a more variable measurement range compared to the determination of specific threshold values.

We thus observed differences between the hair color groups in baseline thermal sensitivity, but not in baseline electrical pain. That responses differed with electrical and thermal stimuli is perhaps unsurprising: it is well established that sensitivity to one type of pain poorly predicts sensitivity to other types of pain as various mechanisms underlie different types of pain.²⁸ An alternative explanation is that electrical stimulation bypasses peripheral transduction mechanism whereas thermal stimulation does not. The observed differences in thermal thresholds could therefore also be due to differences in peripheral transduction rather than (central) processing of pain signals beyond the nociceptors. Despite the fact that the differences in thermal thresholds were statistically significant, the clinical significance remains unclear as the absolute temperature differences between the two groups were quite small.

The pain threshold changes to liposomal lidocaine in this study were comparable to those found in previous studies,^{26,29} but despite a trend towards higher threshold values in the red-hair group, none of the comparisons between the two groups reached statistical significance for liposomal lidocaine. Our most striking finding, though, was that redheads were resistant to anesthesia produced by subcutaneous lidocaine as measured by the pain perception and tolerance thresholds. This outcome is consistent with the anecdotal observations that prompted our study and makes red hair a distinct phenotype associated with local anesthetic sensitivity. However, without a dose-response relationship, it remains unclear whether this represents absolute failure of local anesthetic action or merely a shift of the dose response curve to the right.³⁰ In other words, redheads may simply require more local anesthetic, but ultimately obtain adequate analgesia.

Local anesthetics such as lidocaine prevent transmission of nerve impulses by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.^{31,33} However, the peripheral nervous system is not a known site of MC1R expression.⁶ There is, therefore, no known direct association between MC1R function and peripheral local anesthetic action. In the study by Mogil *et al.*,⁹ women with two variant *MC1R* alleles displayed significantly greater analgesia in response to the kappa-opioid pentazocine compared to those with one or zero variant *MC1R* variant alleles. The authors suggested that involvement of MC1Rs in analgesia could be mediated through MC1Rs expressed in brain glial cells¹¹ and the neurons of the periaqueductal gray,³⁴ a brain area that critically modulates nociception.³⁵ Another possibility is that dysfunctional peripheral *MC1R* mutations produce compensatory upregulation of central melanocortins that in turn increase baseline pain sensitivity via stimulation of melanocortin 4 receptors. Numerous other explanations might be postulated, and currently available information does not provide the basis for identifying a specific mechanism by which *MC1R* mutations might influence pain sensitivity or anesthetic requirement. Whether resistance to local anesthesia is therefore due to central upregulation of melanocortin receptor ligands or some other mechanism remains unknown.

It is well established that women are more sensitive to painful stimuli and require more analgesic medication than men.^{13,15} To reduce variability, we thus restricted this study and a previous one in redheads to women.⁷ Mogil *et al.*⁹ found significant effects of the *MC1R* genotype on pentazocine analgesia, but this effect only emerged in women, which suggests

that the effects of MC1R dysfunction might be gender specific. Whether our results can be extrapolated to men thus remains unknown.

Another limitation of our study is that we did not perform DNA analysis on our volunteers. However, DNA analysis in our previous study⁷ confirmed that all of the red-haired volunteers carried at least one variant *MC1R* allele and that 9 of 10 carried two such alleles, which is consistent with previous reports.^{1,3,36} In contrast 5 of 10 dark haired volunteers carried a single mutant allele and the remaining 5 showed consensus *MC1R* alleles.⁷ It is thus reasonable to assume that virtually all our redheaded volunteers have MC1 receptor dysfunction and equally reasonable to assume that the receptor functions normally in our dark-haired volunteers.

A final limitation is that we were unable to blind investigators (or the subjects!) to hair color. We therefore cannot fully rule out bias on the part of the investigators or evaluate the extent to which our bias may have influenced participants' responses. However, the volunteers were not informed of our hypothesis. They were also fully blinded to temperature readings of the *Neurosensory Analyzer* thermode and *Neurometer* current intensity readings. It thus seems unlikely that bias was the primary explanation for differences we identified between redheads and volunteers with dark hair, especially as differences were only identified under certain conditions.

In summary, redheads are more sensitive to thermal pain than women with dark hair but do not show differences in baseline electrical pain thresholds. Furthermore, redheads are more resistant to the analgesic effects of subcutaneous lidocaine. These results extend the previous observation that redheads are more resistant to volatile anesthetics. Mutations of the melanocortin 1 receptor, or as a consequence thereof, therefore seem to modulate pain sensitivity. It remains unclear whether this modulation occurs at a central or peripheral level or both. An apparent genetic association may not necessarily mean that a straightforward mechanism for the phenotypic effect will be forthcoming. Thus far, these differences seem to be most clearly defined in the presence of drugs (local anesthetic, volatile anesthetic) that suppress responses to noxious stimuli.

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Fig. 1. Pain Tolerance Thresholds to 2000-Hz, 250-Hz, or 5-Hz stimulation on the forearm of volunteers with dark hair (dark, solid lines) or red hair (pale, dashed lines). Three areas of the arm were tested: an untreated control area, an area treated with 4% liposomal lidocaine, and an area injected with 1 mL of 1% lidocaine. Data were plotted as Kaplan-Meier survival curves, and the curves were compared with Log-Rank tests. Y-axis represents the fraction of the study population still able to reach a particular threshold. The curves for the two groups were significantly different for all three frequencies on the area treated subcutaneously with lidocaine.

Table 1.

Demographic and Morphometric Characteristics, Baseline Current Perception, Pain Perception, and Pain Tolerance Thresholds (mA).

		Red Hair	Dark Hair	P
Height (cm)		163 ± 8	161 ± 6	0.25
Weight (kg)		65 ± 11	62 ± 10	0.35
Age (years)		27 ± 5	27 ± 6	0.86
Current Threshold Perception				
	2000 Hz	2.16 ± 0.44	2.02 ± 0.38	0.20
	250 Hz	0.78 ± 0.18	0.74 ± 0.20	0.40
	5 Hz	0.44 ± 0.18	0.46 ± 0.22	0.75
Pain Perception Threshold				
	2000 Hz	6.8 ± 2.8	7.2 ± 3.3	0.60
	250 Hz	2.8 ± 1.3	3.2 ± 2.1	0.33
	5 Hz	1.9 ± 1.1	2.2 ± 1.1	0.35
Pain Tolerance Threshold				
	2000 Hz	10.5 ± 3.8	10.9 ± 4.0	0.68
	250 Hz	4.2 ± 1.7	4.7 ± 2.9	0.42
	5 Hz	2.8 ± 1.4	3.3 ± 1.9	0.27

Data presented as means ± SDs. Comparisons made with unpaired, two-tailed T-tests.

Table 2.
Thermal Perception, Pain Perception, and Pain Tolerance Thresholds.

	Red Hair	Dark Hair	P
Cold Sensory Perception Threshold (°C)	30.7 [30.3, 31.0]	30.5 [29.9, 31.2]	0.596
Cold Pain Perception Threshold (°C)	22.6 [15.1, 26.1]	12.6 [0.0, 20.0]	0.004
Cold Pain Tolerance Threshold (°C)	6.0 [0.0, 9.7]	0.0 [0.0, 2.0]	0.001
Heat Sensory Perception Threshold (°C)	33.8 [33.5, 34.0]	33.5 [33.4, 33.8]	0.015
Heat Pain Perception Threshold (°C)	41.4 [39.7, 43.1]	42.4 [41.3, 44.6]	0.059
Heat Pain Tolerance Threshold (°C)	46.3 [45.7, 47.5]	47.7 [46.6, 48.7]	0.009

Data presented as medians [interquartile range]. Comparisons made with Mann-Whitney rank-sum test.

Table 3.
The Effect of Topical and Subcutaneous Lidocaine on Pain Tolerance Thresholds (mA).

		Red Hair	Dark Hair	P
Control	2000 Hz	5.5 (4.5, 6.5)	6.0 (4.5, 7.5)	0.187
	250 Hz	2.8 (2.4, 3.2)	2.8 (1.6, 4.0)	0.292
	5 Hz	2.0 (1.5, 2.4)	2.1 (1.5, 2.8)	0.708
Liposomal Lidocaine	2000 Hz	7.5 (5.5, 8.5)	9.0 (6.5, 11.5)	0.460
	250 Hz	3.6 (3.2, 6.0)	5.0 (3.2, 6.0)	0.114
	5 Hz	3.2 (2.8, 4.0)	4.5 (3.2, 5.0)	0.106
Subcutaneous Lidocaine	2000 Hz	11.0 (8.5, 16.5)	>20 (14.5, >20)	0.005
	250 Hz	5.0 (4.0, 9.0)	11.6 (8.0, 13.0)	0.003
	5 Hz	6.3 (3.2, 10.2)	8.5 (7.0, 14.2)	0.013

Data presented as median survival thresholds with 95% confidence intervals. Comparison made with Log-rank test.