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Lactate and Pyruvate Content of the Human Cisternal Cerebrospinal Fluid

Normal Values, Age and Sex Dependency, Correlations with Glucose Concentrations

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Summary. Cisternal CSF specimens were obtained from 144 fasted individuals free from organic brain disease (42 males and 102 females; mean age 41±10.3 years, range 16–69 years). In 30 cases a simultaneous lumbar puncture was also performed. The concentration of CSF glucose (Gl) was measured by the o-toluidine method, and that of lactate (La) and pyruvate (Py) by enzymatic tests. No significant difference was found between the mean Gl and Py values of the lumbar and cisternal CSF but the lumbar La was somewhat higher than the cisternal one ($P< 0.10$). In the cisternal CSF the frequency distribution of Gl, La and Py samples was a Gaussian one ($P< 0.05$). The normal ranges, as mean ± 2 SD, were for La 0.680–2.100 m*M*/l, and for Py 0.067–0.141 m*M*/l, respectively. It is proposed that values at the upper and lower limits of the range (between $\bar{x}\pm 2$ SD and $\bar{x}\pm 1$ SD) are considered to be potentially pathological. No significant difference was found between the mean Gl, La and Py values in males and females. Consistent age-related changes could not be detected either in the Gl or Py levels, however, a tendency for La increase was observed in the oldest age-group (over 54 years). A negative correlation was found between the Gl and La concentrations of the cisternal CSF ($r=0.375$; $P< 0.001$).

Key words: Cisternal cerebrospinal fluid – Glucose – Pyruvate – Lactate – Normal values

Zusammenfassung. Es wurden 144 Personen (42 Männer und 102 Frauen, Durchschnittsalter 41,2±10,3 Jahre – 16–69 Jahre) frei von hirnorganischen Erkrankungen untersucht. Zisternale Liquorproben wurden auf nüchternen Magen entnommen und in 30 Fällen wurde gleichzeitig auch eine Lumbalpunktion durchgeführt. Die Konzentration der Glukose (Gl) wurde mit der Orthotoluidinmethode, die des Laktats (La) und Pyruvats (Py) enzymatisch gemessen. Es konnte keine wesentliche Differenz zwischen den Mittelwerten des lumbalen und zisternalen GL und Py gefunden werden, der lumbale

La-Spiegel war aber nahe signifikant höher als der zisternale ($P<0{,}10$). Die statistischen Verteilungen der zisternalen La- und Py-Werte entsprachen der Gaußschen Distribution ($P< 0{,}05$). Als Normbereich ergaben sich für den zisternalen La-Gehalt 0,680–2,100 m*M*/l, und für den Py-Gehalt 0,067–0,141 m*M*/l. Es wird vorgeschlagen, die Bereiche zwischen $\bar{x}\pm 2$ SD und $\bar{x}\pm 1$ SD, im Sinne der sogenannten „grauen Zonen" als untere und obere Grenzzonen zu bezeichnen. Werte, die in diese Grenzzonen fallen, sind als auffällig oder als potentiell pathologisch zu verzeichnen. Keine geschlechtsabhängigen Unterschiede zwischen den Gl-, La- und Py-Werten der Männer und Frauen sowie keine altersabhängigen Änderungen der Gl- und Py-Konzentrationen konnten nachgewiesen werden. Es wurde hingegen eine Erhöhungstendenz des La-Spiegels bei Personen über 54 Jahren gefunden. Zwischen den Gl-und der La-Konzentrationen konnte eine negative Korrelation nachgewiesen werden ($r=-0{,}375$, $P< 0{,}001$).

Introduction

It is generally accepted that lactate (La) and pyruvate (Py) concentrations in the cerebrospinal fluid (CSF) reflect the brain tissue levels of these metabolic intermediates. Therefore La and Py concentrations determined in CSF can provide a measure of cerebral aerobic and anaerobic glycolytic activity [6, 7, 9a, b, 19, 21, 27, 28]. Reliable normal values for these parameters established in human CSF are prerequisites for diagnostic application and further theoretical investigation. In animal studies cisternal levels of La and Py were investigated, whereas in man only the lumbar CSF has been studied. Consequently, normal La levels of lumbar CSF have been reported [5, 10–12, 17, 20, 22–25] with the values established by Kleine and co-workers [10] as the most generally accepted. There are some publications concerning normal values of lumbar Py [5, 13, 17, 20, 25]. However, they are derived from data obtained on relatively small patient groups and none of them is generally accepted (Table 3). Surprisingly, data on La and Py concentrations of human cisternal CSF are completely lacking, nevertheless cisternal fluid could reflect changes in the brain's extracellular space more rapidly and reliably than the lumbar fluid.

The aim of this study was to establish normal values for cisternal La and Py, and to analyse their basic relationships with age and sex. Correlations were also made between Gl and La, Py, and the La/Py ratio. A comparison between Gl, La and Py concentrations of cisternal and lumbar sample-pairs was also performed.

Materials and Methods

Subjects

Individuals included in this study represented a control group for other investigations. The group consisted of 144 persons (42 males and 102 females; mean age $41.2\pm 10{,}3$ years, ranging from 16 to 69 years). The patients were admitted to our neurological department between 1973 and 1981. They were selected from a population having diverse somatic and neurotic complaints and signs which in the majority of cases indicated a neurasthenic syndrome. Patients were assigned for the study according to the following criteria: (1) the existence of an underlying organic brain disease had to be excluded (such lesions were actually detected in 18 poten-

tial candidates); (2) a combination of symptoms diagnostically justifying the investigation both of cisternal and lumbar CSF and—in most cases—pneumoencephalography (PEG); (3) the patient's agreement to the extended examination procedure (see below). Due to the complexity of these criteria, collecting the control group took 8 years, nevertheless approximately 4000 PEGs were carried out in our laboratory during this period.

Each candidate underwent detailed clinical and laboratory investigations. Patients suffering from any manifestly organic brain disease or from metabolic or endocrine disorders known to affect carbohydrate metabolism, as well as persons with marked intellectual deficiency, were not considered for the control group. Also excluded from the study were patients who had gross cerebral atrophy or pathological CSF findings. However, patients with mild widening of the ventricular system and/or of the cortical sulci (16 cases), and persons with moderate cervical and lumbar spondylarthrosis (65 and 52 cases, respectively) and with mild radicular (11 cases) or peripheral symptoms (16 cases) were accepted.

Colleagues not collaborating in this study always proposed the CSF examination and PEG. The patients were informed of the examination procedure and were aware that these investigations jointly served the purposes of scientific research and clinical diagnosis. All persons included agreed to the examination in presence of witnesses.

Sampling Procedure, Analytical Methods and Statistics

Cisternal CSF sampling was always performed in connection with other diagnostic measures. Suboccipital puncture was followed by PEG in 114 cases and by lumbar puncture in 30 cases. In total there were 144 cisternal samples, 30 of which were paired with a simultaneously obtained lumbar sample.

The patients were drug-free, fasted overnight and were not restricted to bedrest. Approximately 5 to 10 min before investigation a cannula (Braun, Melsungen, FRG) was inserted into a cubital vein for sampling venous blood. The suboccipital puncture was carried out between 9 : 00 and 10 : 00 a.m., with the patients in a sitting position. The CSF specimens were promptly centrifuged and stored at 4°C. Analyses were performed on the same day within 5 h of sampling.

The Gl content of CSF and blood was determined by the o-toluidine method [8] and La and Py concentrations were measured by means of enzymatic test-combinations (Boehringer, Mannheim, FRG, Test-Combination Lactate and Test-Combination Pyruvate). The analytical procedures were carried out according to the manufacturers instructions without modification. Coefficients of variation by duplicate measurements were always below 5% for Gl and below 3% for La and Py.

The following statistical methods were employed for data analysis: computation of mean and standard deviation as well as median: Geary's test [18] for distribution analysis; linear regression with the least squares method and calculation of S_{YX} (standard deviation of differences between the observed and calculated y values), and $\sigma_{\bar{y}\cdot\bar{x}}$ (derived as $S_{YX}/\sqrt{n}$); Student's paired and unpaired t-tests [1, 2].

Results

Blood Glucose

The fasting blood level of Gl was found to be 5.958 ± 1.156 m*M*/l (range 3.360–9.389 m*M*/l) in 144 subjects. The mean value is somewhat higher and the range is wider than would be expected in a normal control population under optimal conditions. This may be explained by the fact that many of the patients investigated were expressively anxious.

Cerebrospinal Fluid

Routine Findings. The cell count was below 5 μl both in cisternal and lumbar specimens except in two cisternal samples (where it was found to be 15 and 6/μl,

Table 1. Glucose, lactate and pyruvate concentrations (m*M*/l) in 30 simultaneous cisternal and lumbar CSF specimens

	Mean ± SD		Range		Statistics*
	Cisternal	Lumbar	Cisternal	Lumbar	
Glucose	3.615 ±0.665	3.629 ±0.620	2.589 −5.190	2.794 −5.190	N.S.
Lactate	1.459 ±0.270	1.514 ±0.209	0.819 −1.952	0.960 −2.036	$P < 0.10$
Pyruvate	0.1039 ± 0.0196	0.1048 ± 0.0181	0.0430 − 0.1360	0.0544 − 0.1310	N.S.

* Student's paired *t*-test

respectively). The total protein content exceeded 0.40 g/l in 4 cisternal (0.41–0.50 g/l) and in 5 lumbar (0.43–1.0 g/l) specimens.

Cisterno-lumbar Relations. Average values and ranges of Gl, La and Py measured in 30 cisternal and lumbar CSF samples obtained simultaneously from the same persons are summarized in Table 1. The Gl concentrations in samples from both sites were practically identical and mean values of cisternal and lumbar Py were also very similar. However, the lumbar La level tended to be higher than the cisternal one ($P< 0.10$).

Cisternal CSF

Mean values of Gl, La and Py as well as their ranges as measured in 144 cisternal samples are presented in Table 2. For comparison some data from the literature on normal lumbar La and Py values determined enzymatically are shown in Table 3. Compared with these data, the mean cisternal La was remarkably lower and cisternal Py moderately lower that those of lumbar fluid; however, ranges of both cisternal parameters were considerably broader (expanded towards lower concentrations) than those of lumbar CSF.

Distribution Analysis of the Cisternal La and Pa Values and La/Py Ratios

The La and Py values, as well as La/Py ratios, are shown in Fig. 1; there are six extreme values among the Py data which were judged as outliers and exluded from further analysis. After this correction both La and Py frequency distributions approached a Gaussian form and by testing with Geary's method they proved to be acceptable as normal distributions ($P< 0.05$). The La/Py ratios as quotients of two normally distributed variables of course have a non-normal distribution. Blood and CSF Gl also proved to be normally distributed ($P<0.05$), as was expected.

Normal Values of the Cisternal La and Py Concentrations

If the distribution of a statistical sample obtained on apparently healthy persons approaches a Gaussian one, the limits of the normal range for this variable are to be established conventionally as $\bar{x}+2$ SD and $\bar{x}-2$ SD, respectively [1, 2]. This normal range includes approximately 95% of the group sampled. The normal values of the cisternal La and Py established here are listed in Table 4. Within the conventional normal ranges it seemed to be reasonable to assign an "upper

Table 2. Glucose, lactate and pyruvate concentrations (m*M*/l) in 144 cisternal CSF samples (in parentheses values of pyruvate after excluding 6 extreme data)

	Mean ± SD	Range
Glucose	4.045 ±0.803	2.200 −6.222
Lactate	1.386 ±0.352	0.566 −2.470
Pyruvate	0.1024±0.0226	0.0316−0.1874
	(0.1040±0.0184)	(0.0532−0.1557)

Table 3. Normal values of lactate and pyruvate (m*M*/l) in lumbar CSF from the literature, based on determinations with enzymatic methods

	n	Range	Mean ± SD	Notes	Authors
Lactate	11	1.28 –1.86	1.62 ±0.18		Ponten et al. (1968)
	81	–	1.66 ±0.45	1.3	Pryce et al. (1970)
	83	–	1.48 ±0.31	2.3	
	11	–	1.45 ±0.12	3	Ruscak et al. (1971)
	14	–	1.81 ±0.31		Geraud et al. (1973)
	40	0.80 –2.20	1.55 ±0.42		Sambrook et al. (1973)
	12	1.43 –1.80	1.61 ±0.13		Köhler et al. (1974)
	10	1.43 –1.83	1.62 ±0.91		Schnaberth (1977)
	11	–	1.48 ±0.13		Königshausen et al. (1978)
	142	1.20 –2.10	1.60	4.5	Kleine et al. (1979)
	40	–	1.32 ±0.28		Molnár and Csiba (1981)
Pyruvate	20	0.045–0.125	0.102	3	Lasch (1953)
	11	0.090–0.133	0.110±0.012		Ponten et al. (1968)
	14	–	0.110±0.018		Geraud et al. (1973)
	10	0.090–0.150	0.115±0.018		Schnaberth (1977)
	40	–	0.091±0.014		Molnár and Csiba (1981)

n=number of persons investigated
Notes: 1=values of men; 2=values of women; 3=values given in the original paper as mg/100 ml; 4=average value given as median; 5=data recommended in the Boehringer prospectus as normal values

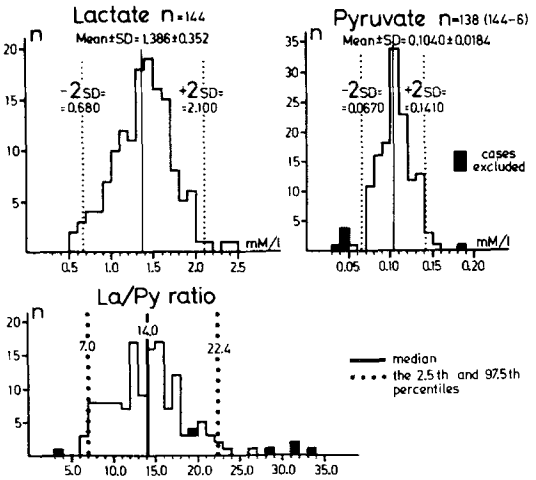

Fig. 1. Distribution of lactate (La) and pyruvate (Py) values and La/Py ratios in the cisternal CSF

Table 4. Normal values of lactate and pyruvate (m*M*/l) in cisternal CSF

	Normal limits ($\bar{x}-2$ SD and $\bar{x}+2$ SD)	"Lower zone" (from $\bar{x}-2$ SD to $\bar{x}-1$ SD)	"Upper zone" (from $\bar{x}+2$ SD to $\bar{x}+1$ SD)
Lactate	0.680 – 2.100	0.680 – 1.030	1.740 – 2.100
Pyruvate	0.067 – 0.141	0.067 – 0.086	0.122 – 0.141

zone" (between the limits $\bar{x}+2$ SD and $\bar{x}+1$ SD) and a "lower zone" (between $\bar{x}-2$ SD and $\bar{x}-1$ SD), respectively. This is further considered in the discussion.

The median of the non-normally distributed La/Py ratios was 14.0 and the extreme values (apart from the excluded cases) were 6.1 and 26.1, respectively. Logically, all La/Py ratios, derived from absolute La and Py values which were considered as non-pathological, must be also accepted as normal. However, there may be an alternative but disputable opinion according to which La/Py ratio could be viewed as an index of the glycolytic activity independently of the individual La and Py concentrations. In order to establish an independent normal range for the La/Py ratios, the method of percentiles may be used, since these are non-normally distributed [1]. Taking the 2.5th and 97.5th percentiles (equivalent to $\bar{x}-2$ SD and $\bar{x}+2$ SD, respectively) as a basis, then 7.0 and 22.4 indicates the limiting values of the "normal" La/Py range.

Age and Sex Dependency

Pryce and co-workers [22] reported that in the lumbar CSF of men La concentration would be higher and Gl concentration lower than in that of women. In cisternal CSF no sex-related differences of Gl, La and Py levels were detected. The tendency for lumbar La to increase with age has been documented by several authors [10, 22, 32]. However, according to Pryce et al. [22] lumbar Gl in those over fifty years old tends to decrease. The relationship between age and the same parameters in the cisternal fluid was also examined, and as seen in Table 5, Gl

Table 5. Comparison of age and glucose, lactate and pyruvate levels ($\bar{x} \pm SD$; m*M*/l) in 144 cisternal CSF samples

Age in years	*n*	Glucose	Lactate	Pyruvate
-24	8	4.154±0.877	1.405±0.493	0.1145±0.0193
25-29	14	4.027±1.078	1.448±0.182	0.1009±0.0157
30-34	19	4.058±0.401	1.318±0.263***	0.1016±0.0270
35-39	23	3.994±0.764	1.418±0.332*	0.1057±0.0262
40-44	20	3.848±0.706	1.325±0.329**	0.0948±0.0176
45-49	28	4.070±0.703	1.296±0.337***	0.0983±0.0233
50-54	20	4.310±0.935	1.397±0.399	0.1068±0.0208
55-	12	3.906±0.590	1.631±0.361	0.1057±0.0154

No consistent age-related changes of glucose and pyruvate levels can be seen. The lactate concentration of the oldest age-group (55-) was compared to each younger group by means of Student's unpaired *t*-test. The significance levels: * = $P < 0.10$; ** = $P < 0.02$; *** = $P < 0.01$

and Py did not show any consistent change related to advancing age. However, cisternal La of those over 54 years old was significantly higher than that found in three younger age groups, and approached significance in a fourth group.

Correlations Between Gl, La and Py Levels

In the cisternal fluid, the correlation between Gl on the one hand, and La, Py or La/Py ratio on the other, was assessed. A negative and highly significant correlation ($r = -0.375$; $P < 0.001$; $S_{YX} = 0.327$ and $\sigma_{\bar{y}\text{-}\bar{x}} = 0.082$) was found between Gl and La as expressed by the following regression equation: $y = -0.165\,x + 2.053$, where y represents the La and x the Gl values (m*M*/l). The Gl concentrations and La/Py ratios were also inversely but not significantly correlated. However, no correlation was found between Gl and Py levels.

Discussion

To select an appropriate group of "apparently healthy" individuals for establishment of the normal value of a body fluid constituent is generally not easy. It is all the more difficult in the case of CSF because like the majority of investigators we also refuse CSF sampling from obviously healthy persons on ethical grounds. However, the neurasthenic syndrome may, as a possible starting point for more serious neurological diseases, necessitate diagnostic measures requiring CSF studies. Patients from this population, who proved to be free from organic brain diseases, were included in our control group. The term "organic brain disease" was conventionally interpreted and applied here mainly on a morphological basis.

Blood glucose levels must be taken into account when investigating Gl and glycolytic intermediates in CSF, because Gl is transferred into CSF from the blood by a carrier mediated transport mechanism [4]. Alterations in blood Gl could influence not only CSF Gl levels but also La and Py concentrations [22, 29, 30]. This fact could be a potential source of minor error in our material where

blood Gl levels varied somewhat from those expected in a fasted normal population. The broader distribution of blood Gl was not caused by including individuals with diabetes mellitus but it could be explained by vegetative dysregulation and anxiety. The latter was a common symptom in the majority of the cases but in this investigation it was also connected with apprehension concerning the PEG process, believed to be very painful.

Routine findings in the cisternal and lumbar CSF specimens such as cell count, total protein, globulin reactions, etc., were essentially normal. However, higher total protein levels in five lumbar samples caused by spondylarthrosis were measured, but since no correlation could be found between these and Gl, La or Py concentrations, it seems that the higher protein values have no significance in the present context.

In 1938 Merritt and Fremont-Smith [15] reviewed a series of papers reporting a decreasing ventriculo-cisterno-lumbar Gl concentration gradient of 6–18 mg/-100 ml. This was explained by Gl consumption of tissues adjacent to the fluid spaces. It was interesting that our results could not confirm the existence of a steady cisterno-lumbar Gl gradient in a population of mobile, fasted individuals. However, in the cited literature most patients who underwent a duplicate fluid sampling (lumbar and ventricular or lumbar and cisternal punctures) were suffering from some organic brain disease, and the withdrawal of CSF was often connected with local anesthesia and operative interventions. It is clear that if such an intervention induces a sudden increase in blood Gl and consecutively in the Gl content of newly secreted CSF, this will occur more rapidly in the cranial space than in the spinal space. In such a way a temporary gradient can develop especially in immobilized patients. This gradient, however, does not seem to exist in individuals with near constant blood Gl levels.

The cisternal and lumbar CSF Py values differed only slightly whereas La level tended to be higher in lumbar than in cisternal fluid. The mean La and more particularly Py values measured *in 144 cisternal specimens* were only somewhat lower but their ranges were considerably wider than those for lumbar fluid reported in the literature (Table 3). A possible explanation is as follows: Recently it has been demonstrated that various functional activities such as speaking, reading, solving visual tasks, or simply, changes in illumination are accompanied by rapid and considerable changes in Gl consumption and regional blood flow of the cerebral structures involved [14, 16, 26]. It is reasonable to assume that these oscillatory functional changes in the Gl consumption and glycolytic activity of the brain will be quickly reflected in CSF La and Py concentrations of the cranial space. However, these changes in the metabolite levels will be reduced and delayed in the spinal space because of mixing and slow bulk flow of CSF.

To our knowledge there is no report available on a distribution analysis of CSF La and Py levels. We found that in cisternal CSF both parameters proved to be normally distributed. On the basis of the Gaussian distribution we were able to establish the normal ranges for both parameters by means of the so-called "2 sigma rule". Within the conventional normal ranges it seemed justifiable to assess an "upper zone" (between $\bar{x}+2$ SD and $\bar{x}+1$ SD) and a "lower zone" (between $\bar{x}-2$ SD and $\bar{x}-1$ SD). Both zones include approximately 13.5% of the population accepted as normal, above and below the central 68%. The reasons for

setting such limits are as follows. For most constituents tested in clinical chemistry there is an overlap of values obtained from the normal and abnormal populations. That is why all kinds of normal values expressed as a single range involve two types of inherent errors: (1) a number of normal persons (such as "individual variants" or "subjects in special functional states", etc.) would fall outside the range and would be considered to be pathological, (2) some of the abnormal values, on the other hand, would fall in the normal range (at the limits) and go undetected. Therefore it has been proposed that two normal ranges be used [31]. The inner range would include 80% of the normal values and all findings falling into this range would be considered as definitely normal. The larger range would include approximately 98% of the apparently normal population and any value outside this range would be considered as definitely abnormal. Values falling within the range of 80% and 98% constitute a "grey zone" and these values would be suspected of abnormality. On the other hand normal ranges used in practice would be unnecessarily broad due to inadvertent inclusion of abnormal values derived from individuals suffering from subclinical diseases. Therefore it has been proposed that we should accept only the narrow range of truly healthy young people as ideal [3]. Such considerations and criticism of the concept of normal ranges are especially relevant in CSF chemistry where the selection of the normal population is complicated by ethical, medical and practical problems.

In a neurasthenic population such as our control group, certain mental and emotional conditions might also induce changes in GI breakdown. However, according to present knowledge it cannot be unequivocally decided whether such a change is acceptable as normal or must be considered as pathological. Errors deriving from this uncertainty can be reduced by setting edge zones. We think that data falling in the central 68% can be unequivocally considered as normal, whereas findings falling into the upper or lower zone would qualify as cases for special attention or potentially pathological ones. To set limits for these zones the standard deviation can serve as a natural measure in a normally distributed population, instead of percentage figures chosen arbitrarily [31].

It is noteworthy that in cisternal CSF the upper value limiting the whole normal range is three times greater than the lower one in the case of La, while only twice greater for Py, because variations in La levels are greater than those in Py levels.

Physiological variations of the La/Py ratio are also considerably wide in cisternal CSF, with ranges from 6.1 to 26.1 being considered as non-pathological. In our opinion, this quotient should always be evaluated in relation to the La and Py concentrations.

Since the proportion of older people was relatively small in our control group, it was not appropriate to analyse for age-dependent phenomena. In lumbar CSF a continuous increase in the La concentration as a function of advancing age was described [10, 32]. We could not demonstrate such a continuous change in the cisternal fluid. A tendency for La increase was found only in the group of individuals older than 54 years of age. This was probably caused by subclinical atherosclerotic cerebrovascular changes.

Between cisternal Gl and La a negative, and highly significant, correlation was observed as had been demonstrated on a smaller patient group in our previous work [30]. Yesavage and Berger [32] found the same relation in the lumbar fluid of fasted volunteers but it was not statistically significant. In contrast to these findings, a positive Gl versus La correlation was observed postprandially in the lumbar fluid [22], and after Gl loading in cisternal CSF [30]. It seems that Gl transport could be relatively insufficient for glycolysis in the fasting state, whereas in the case of enhanced Gl supply a parallelism between Gl availability and La production occurs.

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